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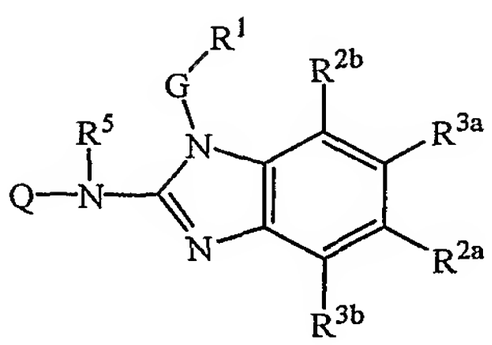
(54) Title: AMINO-BENZIMIDAZOLES DERIVATIVES AS INHIBITORS OF RESPIRATORY SYNCYTIAL VIRUS REPLICATION



(I)

(57) Abstract: The present invention concerns amino-benzimidazoles having inhibitory activity on the replication of the respiratory syncytial virus and having the formula (I) their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms wherein Q is Ar_1 or C_{1-6}alkyl substituted with one or more substituents selected from trifluoromethyl, C_{3-7}cycloalkyl, Ar^2, hydroxy, C_{1-4}alkoxy, C_{1-4}alkylthio, Ar^2-oxy-, Ar^2-thio-, $Ar^2(CH2)_{,,}$oxy, $Ar^2(CH_2)_n$thio, hydroxycarbonyl, aminocarbonyl, C_{1-4} alkylcarbonyl, Ar^2carbonyl, C_{1-4}alkoxycarbonyl, $Ar^2(CH_2)_n$ carbonyl, aminocarbonyloxy, C_{1-4} alkylcarbonyloxy, Ar^2carbonyloxy, $Ar^2(CH_2)_n$carbonyloxy, hydroxy-C_{2-4}-alkyloxy, C_{1-4} alkoxycarbonyl$(CH_2)_n$oxy, monoor di(C_{1-4}alkyl)-aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyloxy, aminosulfonyl, mono- or di(C_{1-4}alkyl)aminosulfonyl, dioxolanyl optionally substituted with one or two C_{1-6}alkyl radicals, and a heterocycle selected from pyrrolidinyl, pyrrolyl, dihydropyrrolyl, thiazolidinyl, imidazolyl, triazolyl, piperidinyl, homopiperidinyl, piperazinyl, pyridyl and tetrahydropyridyl, which each may optionally be substituted with oxo or C_{1-6}alkyl; G is a direct bond or optionally substituted C_{1-10}alkanediyl R^1 is Ar^1 or a monocyclic or bicyclic heterocycle; one of R^{2a} and R^{3a} is C_{1-6}alkyl and the other one of R^2a and R^{3a} is hydrogen; in case R^2a is different from hydrogen then R^{2b} is hydrogen or C_{1-6}alkyl, and R^{3b} is hydrogen; in case R^{3a} is different from hydrogen then R^{3b} is hydrogen or C $_{1-6}$alkyl, and R^{2b} is hydrogen; Ar^1 is phenyl or substituted phenyl and Ar^2 is phenyl or substituted phenyl. It further concerns their preparation and compositions comprising them, as well as their use as a medicine.

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AMINO-BENZIMIDAZOLES DERIVATIVES AS INHIBITORS OF RESPIRATORY SYNCYTIAL VIRUS REPLICATION

The present invention is concerned with amino-benzimidazole derivatives having antiviral activity, in particular, having an inhibitory activity on the replication of the respiratory syncytial virus (RSV). It further concerns their preparation and compositions comprising them, as well as their use as a medicine.

Human RSV or Respiratory Syncytial Virus is a large RNA virus, member of the family of Paramyxoviridae, subfamily pneumoviridae together with bovine RSV virus. Human RSV is responsible for a spectrum of respiratory tract diseases in people of all ages throughout the world. It is the major cause of lower respiratory tract illness during infancy and childhood. Over half of all infants encounter RSV in their first year of life, and almost all within their first two years. The infection in young children can cause lung damage that persists for years and may contribute to chronic lung disease in later life (chronic wheezing, asthma). Older children and adults often suffer from a (bad) common cold upon RSV infection. In old age, susceptibility again increases, and RSV has been implicated in a number of outbreaks of pneumonia in the aged resulting in significant mortality.

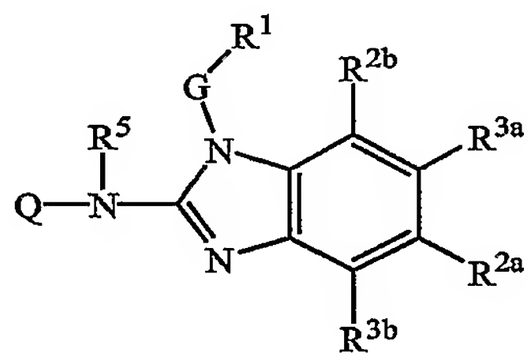
Infection with a virus from a given subgroup does not protect against a subsequent infection with an RSV isolate from the same subgroup in the following winter season. Re-infection with RSV is thus common, despite the existence of only two subtypes, A and B.

Today only three drugs have been approved for use against RSV infection. A first one is ribavirin, a nucleoside analogue, provides an aerosol treatment for serious RSV infection in hospitalized children. The aerosol route of administration, the toxicity (risk of teratogenicity), the cost and the highly variable efficacy limit its use. The other two drugs, RespiGam® and palivizumab, polyclonal and monoclonal antibody immunostimulants, are intended to be used in a preventive way.

Other attempts to develop a safe and effective RSV vaccine have all met with failure thus far. Inactivated vaccines failed to protect against disease, and in fact in some cases enhanced disease during subsequent infection. Life attenuated vaccines have been tried with limited success. Clearly there is a need for an efficacious non-toxic and easy to administer drug against RSV replication.

Benzimidazoles and imidazopyridines as inhibitors of RSV replication have been described in WO 01/00611, WO 01/00612 and WO 01/00615.

The present invention concerns inhibitors of RSV replication, which can be represented by formula (I):



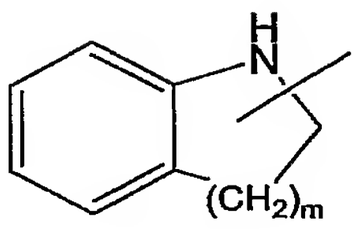
(I)

their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms wherein

Q is Ar^2, C_{3-7}cycloalkyl, or C_{1-6}alkyl substituted with one or more substituents each independently selected from the group consisting of trifluoromethyl, C_{3-7}cycloalkyl, Ar^2, hydroxy, C_{1-4}alkoxy, C_{1-4}alkylthio, Ar^2-oxy-, Ar^2-thio-, $Ar^2(CH_2)_n$oxy, $Ar^2(CH_2)_n$thio, hydroxycarbonyl, aminocarbonyl, C_{1-4}alkyl-carbonyl, Ar^2carbonyl, C_{1-4}alkoxycarbonyl, $Ar^2(CH_2)_n$carbonyl, aminocarbonyl-oxy, C_{1-4}alkylcarbonyloxy, Ar^2carbonyloxy, $Ar^2(CH_2)_n$carbonyloxy, hydroxy-C_{2-4}-alkyloxy, C_{1-4}alkoxycarbonyl$(CH_2)_n$oxy, mono- or di(C_{1-4}alkyl)amino-carbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyloxy, aminosulfonyl, mono- or di(C_{1-4}alkyl)aminosulfonyl, dioxolanyl optionally substituted with one or two C_{1-6}alkyl radicals, and a heterocycle selected from the group consisting of pyrrolidinyl, pyrrolyl, dihydropyrrolyl, indolyl, imidazolyl, triazolyl, piperidinyl, homopiperidinyl, piperazinyl, pyridyl and tetrahydropyridyl, wherein each of said heterocycle may optionally be substituted with oxo or C_{1-6}alkyl;

G is a direct bond or C_{1-10}alkanediyl optionally substituted with one or more substituents individually selected from the group consisting of hydroxy, C_{1-6}alkyloxy, Ar^1C_{1-6}alkyloxy, C_{1-6}alkylthio, Ar^1C_{1-6}alkylthio, $HO(-CH_2-CH_2-O)_n$-, C_{1-6}alkyloxy$(-CH_2-CH_2-O)_n$- and Ar^1C_{1-6}alkyloxy$(-CH_2-CH_2-O)_n$-;

R^1 is Ar^1 or a monocyclic or bicyclic heterocycle being selected from piperidinyl, piperazinyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, tetrahydro-furanyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, isothiazolyl, pyrazolyl, isoxazolyl, oxadiazolyl, quinolinyl, quinoxalinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, pyridopyridyl, naphthiridinyl, 1*H*-imidazo[4,5-b]pyridinyl, 3*H*-imidazo[4,5-b]pyridinyl, imidazo[1,2-a]-pyridinyl, 2,3-dihydro-1,4-dioxino[2,3-b]pyridyl and a radical of formula



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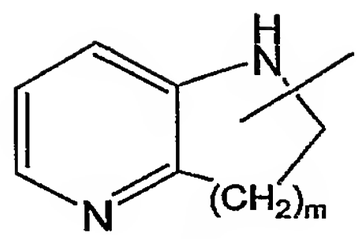

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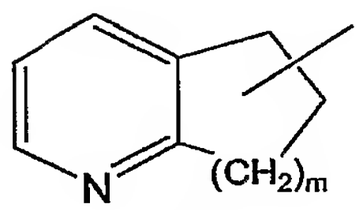

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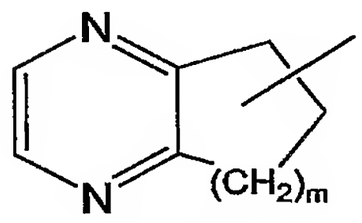

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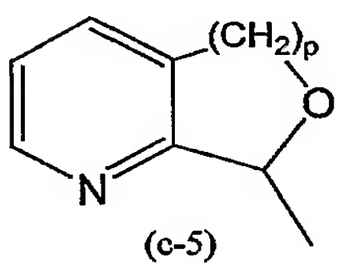

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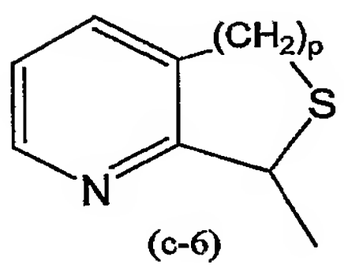

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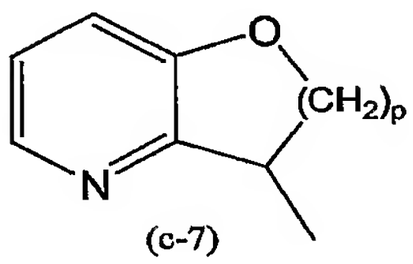

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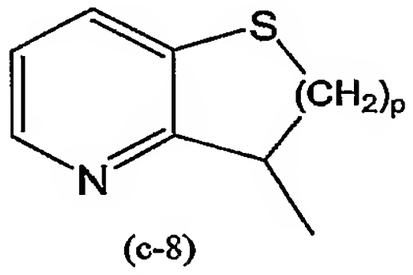

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;

wherein each of said monocyclic or bicyclic heterocycles may optionally be substituted with 1 or where possible more, such as 2, 3, 4 or 5, substituents individually selected from the group of substituents consisting of halo, hydroxy, amino, cyano, carboxyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, Ar^1, Ar^1C_{1-6}alkyl, Ar^1C_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{4a}-, Ar^1-SO_2-NR^{4a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{4a}R^{4b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, Ar^1C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-;

each n independently is 1, 2, 3 or 4;

one of R^{2a} and R^{3a} is C_{1-6}alkyl and the other one of R^{2a} and R^{3a} is hydrogen;

in case R^{2a} is different from hydrogen then R^{2b} is hydrogen or C_{1-6}alkyl, and R^{3b} is hydrogen;

in case R^{3a} is different from hydrogen then R^{3b} is hydrogen or C_{1-6}alkyl, and R^{2b} is hydrogen; or

R^{2a}, R^{2b}, R^{3a} and R^{3b} all are hydrogen;

R^{4a} and R^{4b} can be the same or can be different relative to one another, and are each independently hydrogen or C_{1-6}alkyl; or

R^{4a} and R^{4b} taken together may form a bivalent radical of formula -(CH_2)$_s$-;

R^5 is hydrogen or C_{1-6}alkyl;

m is 1 or 2;

p is 1 or 2;

s is 4 or 5

Ar^1 is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, and C_{1-6}alkyloxy;

Ar^2 is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from the group consisting of halo, hydroxy, amino, cyano, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxy, aminosulfonyl, aminocarbonyl, hydroxycarbonyl, C_{1-4}alkylcarbonyl, mono- or di(C_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyl)aminocarbonyl, mono- or di(C_{1-4}alkyl)-aminosulfonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl and C_{1-4}alkoxycarbonyl.

The invention relates to the use of a compound of formula (I), or a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex and stereochemically isomeric form thereof, for the manufacture of a medicament for inhibiting RSV replication. Or the invention relates to a method of inhibiting RSV replication in a warm-blooded animal said method comprising the administration of an effective amount of a compound of formula (I), or a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex and stereochemically isomeric form thereof.

In a further aspect, this invention relates to novel compounds of formula (I) as well as methods for preparing these compounds.

The term 'prodrug' as used throughout this specification and claims means the pharmacologically acceptable derivatives, e.g. esters and amides, such that the resulting biotransformation product of the derivative is the active drug as defined in the compounds of formula (I). The reference by Goodman and Gilman (The Pharmacological Basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs", p. 13-15) describing prodrugs generally, is hereby incorporated. Prodrugs are characterized by a good aqueous solubility and bioavailability, and are readily metabolized into the active inhibitors *in vivo*.

The terms 'C_{1-6}alkyl optionally substituted with one or more substituents' such as used in the definition of Q, or 'C_{1-10}alkanediyl optionally substituted with one or more substituents' as used in the definition of G are meant to comprise C_{1-6}alkyl radicals respectively C_{1-10}alkanediyl radicals having no, one, two or more substituents, for example no, one, two, three, four, five or six substituents, in particular no, one, two or three substituents, further in particular no, one or two substituents. The upper limit of the number of substituents is determined by the number of hydrogen atoms that can be

replaced as well as by the general properties of the substituents such as their bulkiness, these properties allowing the skilled person to determine said upper limit.

As used herein in relation to Q, the term 'wherein each of said heterocycle may optionally be substituted with oxo or C_{1-6}alkyl' is meant to comprise heterocycles substituted with one or more, such up to 3, or up to 2 substituents or with one substituent indepently selected from oxo and C_{1-6}alkyl.

As used in the foregoing and hereinafter, 'polyhaloC_{1-6}alkyl' as a group or part of a group, e.g. in polyhaloC_{1-6}alkyloxy, is defined as mono- or polyhalo substituted C_{1-6}alkyl, in particular C_{1-6}alkyl substituted with up to one, two, three, four, five, six, or more halo atoms, such as methyl or ethyl with one or more fluoro atoms, for example, difluoromethyl, trifluoromethyl, trifluoroethyl. Also included are perfluoro C_{1-6}alkyl groups, which are C_{1-6}alkyl groups whereion all hydrogen atoms are replaced by fluoro atoms, e.g. pentafluoroethyl. In case more than one halogen atom is attached to an alkyl group within the definition of polyhaloC_{1-4}alkyl, the halogen atoms may be the same or different.

Each of the monocyclic or bicyclic heterocycles in the definition of R^1 may optionally be substituted with 1 or where possible more substituents, such as 2, 3, 4 or 5, substituents. In particular, said heterocycles may optionally be substituted with up to 4, up to 3, up to 2 substituents, or up to 1 substituent.

Each Ar^1 or Ar^2 may be unsubstituted phenyl or phenyl substituted with 1 or more substituents, such as 5 or 4 substituents or, which is preferred, up to 3 substituents, or up to two substituents, or with one substituent.

A hydroxyC_{1-6}alkyl group when substituted on an oxygen atom or a nitrogen atom preferably is a hydroxyC_{2-6}alkyl group wherein the hydroxy group and the oxygen or nitrogen is separated by at least two carbon atoms.

As used herein C_{1-3}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 3 carbon atoms such as methyl, ethyl, propyl, 1-methylethyl and the like; C_{1-4}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as the group defined for C_{1-3}alkyl and butyl and the like; C_{2-4}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 2 to 4 carbon atoms such as ethyl, propyl, 1-methylethyl, butyl

and the like; C_{1-5}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 5 carbon atoms such as the groups defined for C_{1-4}alkyl and pentyl, 1-methylbutyl, 2-methylbutyl, 1-ethylpropyl and the like; C_{1-6}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as the groups defined for C_{1-5}alkyl and , hexyl, 2-methylpentyl, 3-methylpentyl and the like; C_{1-9}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 9 carbon atoms such as the groups defined for C_{1-6}alkyl and heptyl, octyl, nonyl, 2-methylhexyl, 2-methylheptyl and the like; C_{1-10}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 10 carbon atoms such as the groups defined for C_{1-9}alkyl and decyl, 2-methylnonyl and the like.

C_{3-7}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

C_{2-5}alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 2 to 5 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,2-propanediyl, 2,3-butanediyl, 1,5-pentanediyl and the like, C_{1-4}alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the like; C_{1-6}alkanediyl is meant to include C_{1-4}alkanediyl and the higher homologues thereof having from 5 to 6 carbon atoms such as, for example, 1,5-pentanediyl, 1,6-hexanediyl and the like; C_{1-10}alkanediyl is meant to include C_{1-6}alkanediyl and the higher homologues thereof having from 7 to 10 carbon atoms such as, for example, 1,7-heptanediyl, 1,8-octanediyl, 1,9-nonanediyl, 1,10-decanediyl and the like.

As used herein before, the term (=O) forms a carbonyl moiety when attached to a carbon atom, a sulfoxide moiety when attached to a sulfur atom and a sulfonyl moiety when two of said terms are attached to a sulfur atom. The term (=N-OH) forms a hydroxylimine moiety when attached to a carbon atom.

The term halo is generic to fluoro, chloro, bromo and iodo.

It should be noted that the radical positions on any molecular moiety used in the definitions may be anywhere on such moiety as long as it is chemically stable.

Radicals used in the definitions of the variables include all possible isomers unless otherwise indicated. For instance pyridyl includes 2-pyridyl, 3-pyridyl and 4-pyridyl; pentyl includes 1-pentyl, 2-pentyl and 3-pentyl.

When any variable occurs more than one time in any constituent, each definition is independent.

Whenever used hereinafter, the term 'compounds of formula (I)', or 'the present compounds' or similar term is meant to include the compounds of general formula (I), their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms. An interesting subgroup of the compounds of formula (I) or any subgroup thereof are the *N*-oxides, salts and all the stereoisomeric forms of the compounds of formula (I).

It will be appreciated that some of the compounds of formula (I) may contain one or more centers of chirality and exist as stereochemically isomeric forms.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of formula (I) may possess.

Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of the present invention both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

Pure stereoisomeric forms of the compounds and intermediates as mentioned herein are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure of said compounds or intermediates. In particular, the term 'stereoisomerically pure' concerns compounds or intermediates having a stereoisomeric excess of at least 80% (i. e. minimum 90% of one isomer and maximum 10% of the other possible isomers) up to a stereoisomeric excess of 100% (i.e. 100% of one isomer and none of the other), more in particular, compounds or intermediates having a stereoisomeric excess of 90% up to 100%, even more in particular having a stereoisomeric excess of 94% up to 100% and most in particular having a stereoisomeric excess of 97% up to 100%. The terms 'enantiomerically pure' and

'diastereomerically pure' should be understood in a similar way, but then having regard to the enantiomeric excess, respectively the diastereomeric excess of the mixture in question.

Pure stereoisomeric forms of the compounds and intermediates of this invention may be obtained by the application of art-known procedures. For instance, enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids or bases. Examples thereof are tartaric acid, dibenzoyl-tartaric acid, ditoluoyltartaric acid and camphosulfonic acid. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably, if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The diastereomeric racemates of formula (I) can be obtained separately by conventional methods. Appropriate physical separation methods that may advantageously be employed are, for example, selective crystallization and chromatography, e.g. column chromatography.

For some of the compounds of formula (I), their prodrugs, N-oxides, salts, solvates, quaternary amines, or metal complexes and the intermediates used in the preparation thereof, the absolute stereochemical configuration was not experimentally determined. A person skilled in the art is able to determine the absolute configuration of such compounds using art-known methods such as, for example, X-ray diffraction.

The present invention is also intended to include all isotopes of atoms occurring on the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

For therapeutic use, salts of the compounds of formula (I) are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases, which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable acid and base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and base addition salt forms which the compounds of formula (I) are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic (i.e. hydroxybutanedioic acid), tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

The compounds of formula (I) containing an acidic proton may also be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

The term "quaternary amine" as used hereinbefore defines the quaternary ammonium salts which the compounds of formula (I) are able to form by reaction between a basic nitrogen of a compound of formula (I) and an appropriate quaternizing agent, such as, for example, an optionally substituted alkyl halide, aryl halide or arylalkyl halide, e.g. methyl iodide or benzyl iodide. Other reactants with good leaving groups may also be used, such as alkyl trifluoromethanesulfonates, alkyl methanesulfonates, and alkyl p-toluenesulfonates. A quaternary amine has a positively charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate and acetate. The counterion of choice can be introduced using ion exchange resins.

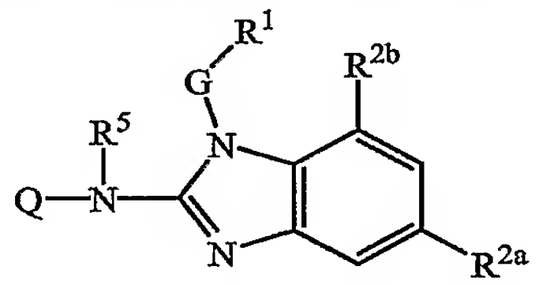
The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

It will be appreciated that the compounds of formula (I) may have metal binding, chelating, complex forming properties and therefore may exist as metal complexes or metal chelates. Such metalated derivatives of the compounds of formula (I) are intended to be included within the scope of the present invention.

Some of the compounds of formula (I) may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

Any subgroup of compounds of formula (I) specified herein is meant to also comprise the prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms of this subgroup of compounds of formula (I).

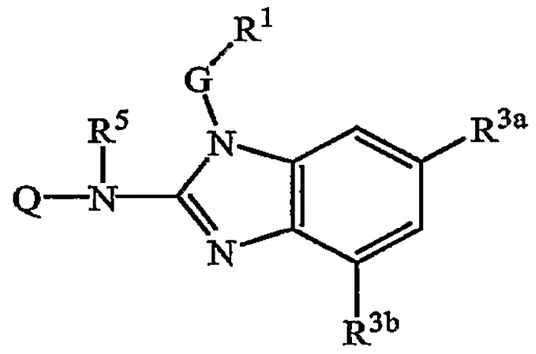
One embodiment of the present invention concerns compounds of formula (I-a):



(I-a)

wherein Q, R^5, G and R^1 are as specified above or as in any of the subgroups of compounds specified herein; and
R^{2a} is C_{1-6}alkyl;
R^{2b} is hydrogen or C_{1-6}alkyl.

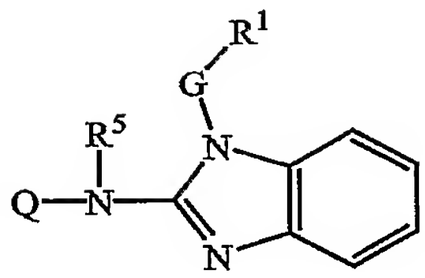
Another embodiment of the present invention concerns compounds of formula (I-b):



(I-b)

wherein Q, R^5, G and R^1 are as specified above or as in any of the subgroups of compounds specified herein; and
R^{3a} is C_{1-6}alkyl;
R^{3b} is hydrogen or C_{1-6}alkyl.

Another embodiment of the present invention concerns compounds of formula (I-c):



(I-c)

wherein Q, R^5, G and R^1 are as specified above or as in any of the subgroups of compounds specified herein.

It is to be understood that the above defined subgroups of compounds of formulae (I-a), (I-b), etc. as well as any other subgroup defined herein, are meant to also comprise any prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms of such compounds.

Particular subgroups of the compounds of formula (I) are those compounds of formula (I), or any subgroup of compounds of formula (I) specified herein, wherein G is C_{1-10}alkanediyl, more in particular wherein G is methylene.

Other particular subgroups of the compounds of formula (I) are those compounds of formula (I), or any subgroup of compounds of formula (I) specified herein, wherein
(a) R^1 is other than Ar^1; or wherein
(b) R^1 is Ar^1 or a monocyclic heterocycle, which is as specified in the definitions of the compounds of formula (I) or any of the subgroups thereof.

Further particular subgroups of the compounds of formula (I) are those compounds of formula (I), or any subgroup of compounds of formula (I) specified herein, wherein
(c) R^1 is pyridyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of halo, hydroxy, amino, cyano, carboxyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, Ar^1, Ar^1C_{1-6}alkyl, Ar^1C_{1-6}alkyl-oxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)amino-C_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{4a}-, Ar^1-SO_2-NR^{4a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{4a}R^{4b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, Ar^1C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-; or more in particular
(d) R^1 is pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of hydroxy, C_{1-6}alkyl, halo, C_{1-6}alkyloxy, Ar^1C_{1-6}alkyloxy and (C_{1-6}alkyloxy)C_{1-6}alkyloxy; preferably wherein
(e) R^1 is pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of hydroxy, C_{1-6}alkyl, halo and C_{1-6}alkyloxy; or wherein

(f) R^1 is pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of hydroxy and C_{1-6}alkyl; more preferably wherein

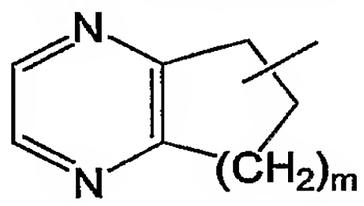
(g) R^1 is pyridyl substituted with hydroxy and C_{1-6}alkyl; or more preferably wherein

(h) R^1 is pyridyl substituted with hydroxy and methyl; or wherein

(i) R^1 is 3-hydroxy-6-methylpyrid-2-yl.

Further embodiments comprise those compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein

(j) R^1 is Ar^1, quinolinyl, benzimidazolyl, a radical of formula



(c-4)

pyrazinyl, or pyridyl; or wherein

(k) R^1 is Ar^1, quinolinyl, benzimidazolyl or a radical of formula (c-4) wherein m is 2, pyrazinyl, or pyridyl;

wherein each of the radicals in (j) and (k) may optionally be substituted with the substituents specified in the definition of the compounds of formula (I) and in particular pyridyl may be substituted as specified above in (a) to (i).

Further embodiments comprise those compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein

(l) R^1 is Ar^1, quinolinyl, benzimidazolyl or a radical of formula (c-4) wherein m is 2, pyrazinyl, or pyridyl, wherein each of these radicals may optionally be substituted with one, two or three radicals selected from the group consisting of halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^1C_{1-6}alkyloxy, (C_{1-6}alkyloxy)C_{1-6}alkyloxy; or more specifically wherein

(m) R^1 is Ar^1, quinolinyl, benzimidazolyl or a radical of formula (c-4) wherein m is 2, pyrazinyl, or pyridyl, wherein each of these radicals may optionally be substituted with one, two or three radicals selected from the group consisting of halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, benzyloxy; or more specifically wherein

(n) R^1 is phenyl optionally substituted with one, two or three radicals selected from the group consisting of halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy; quinolinyl; a radical (c-4) wherein m is 2, optionally substituted with up to two radicals selected from C_{1-6}alkyl; benzimidazolyl optionally substituted with C_{1-6}alkyl; pyridyl optionally substituted with one or two radicals selected from hydroxy, halo, C_{1-6}alkyl, benzyloxy and C_{1-6}alkyloxy, pyrazinyl optionally substituted with up to three

radicals selected from C_{1-6}alkyl; or pyridyl substituted or optionally substituted as specified above in (a) – (i); or wherein

(o) R^1 is phenyl optionally substituted with one or two radicals selected from the group consisting of halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy; or

(p) R^1 is quinolinyl; or

(q) R^1 is a radical (c-4) wherein m is 2, optionally substituted with up to two radicals selected from C_{1-6}alkyl; or

(r) R^1 is benzimidazolyl optionally substituted with C_{1-6}alkyl; pyridyl optionally substituted with one or two radicals selected from hydroxy, halo, C_{1-6}alkyl, benzyloxy and C_{1-6}alkyloxy; or

(s) R^1 is pyrazinyl optionally substituted with up to three radicals selected from C_{1-6}alkyl.

Preferred subgroups of compounds of formula (I) or any of the subgroups of compounds of formula (I) are those wherein G is a direct bond or methylene and R^1 is as specified above in (a) – (s). Further preferred are the compounds of formula (I) or any of the subgroups specified herein wherein G is a direct bond and R^1 is a radical (c-4), in particular wherein m is 2, optionally substituted with up to two radicals selected from C_{1-6}alkyl. Further preferred are the compounds of formula (I) or any of the subgroups specified herein wherein or G is methylene and R^1 is as specified above in (a) – (s), but is other than a radical (c-4).

Other embodiments comprise those compounds of formula (I) or any of the subgroups of compounds of formula (I) specified herein, wherein R^5 is hydrogen.

Other embodiments comprise those compounds of formula (I) or any of the subgroups of compounds of formula (I) specified herein, wherein:

(a) Q is Ar^2, C_{3-7}cycloalkyl or C_{1-6}alkyl substituted with one or two substituents each independently selected from the group consisting of substituents mentioned in the definition of the compounds of formula (I) or of any subgroup thereof; or in particular

(b) Q is Ar^2, C_{3-7}cycloalkyl or C_{1-6}alkyl substituted with one substituent selected from the group consisting of substituents mentioned in the definition of the compounds of formula (I) or of any subgroup thereof, and said C_{1-6}alkyl is optionally further substituted with one hydroxy; or

(c) Q is Ar^2, C_{3-7}cycloalkyl, or C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from the group consisting of trifluoro-methyl, Ar^2, hydroxy, C_{1-4}alkoxy, C_{1-4}alkylthio, Ar^2-oxy-, $Ar^2(CH_2)_n$oxy, hydroxy-

carbonyl, aminocarbonyl, C_{1-4}alkylcarbonyl, Ar^2carbonyl, C_{1-4}alkoxycarbonyl, C_{1-4}alkylcarbonyloxy, hydroxy-C_{2-4}-alkyloxy, mono- or di(C_{1-4}alkyl)amino-carbonyl, dioxolanyl optionally substituted with one or two C_{1-6}alkyl radicals, and a heterocycle selected from the group consisting of pyrrolidinyl, pyrrolyl, dihydropyrrolyl, indolyl, imidazolyl, triazolyl, piperidinyl, homopiperidinyl, piperazinyl, pyridyl and tetrahydropyridyl, wherein each of said heterocycle may optionally be substituted with up to two substituents independently selected from oxo and C_{1-6}alkyl; or

(d) Q is Ar^2, C_{3-7}cycloalkyl, or C_{1-6}alkyl optionally substituted with one substituent selected from trifluoromethyl, Ar^2, hydroxy, C_{1-4}alkoxy, C_{1-4}alkylthio, Ar^2-oxy-, $Ar^2(CH_2)_n$oxy, hydroxycarbonyl, aminocarbonyl, C_{1-4}alkylcarbonyl, Ar^2carbonyl, C_{1-4}alkoxycarbonyl, C_{1-4}alkylcarbonyloxy, hydroxy-C_{2-4}-alkyloxy, mono- or di(C_{1-4}alkyl)-aminocarbonyl, dioxolanyl optionally substituted with one or two C_{1-6}alkyl radicals, and a heterocycle selected from the group consisting of pyrrolidinyl, pyrrolyl, dihydropyrrolyl, indolyl, imidazolyl, triazolyl, piperidinyl, homopiperidinyl, piperazinyl, pyridyl and tetrahydropyridyl, wherein each of said heterocycle may optionally be substituted with up to two substituents independently selected from oxo and C_{1-6}alkyl, and said C_{1-6}alkyl is optionally further substituted with one hydroxy; or

(e) Q is Ar^2, C_{3-7}cycloalkyl, or C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from the group consisting of Ar^2, hydroxy, C_{1-4}alkoxy, C_{1-4}alkylthio, aminocarbonyl, C_{1-4}alkoxycarbonyl, hydroxy-C_{2-4}-alkyloxy, dioxolanyl substituted with two C_{1-6}alkyl radicals, and a heterocycle selected from the group consisting of pyrrolidinyl, indolyl, imidazolyl, piperidinyl, piperazinyl, and pyridyl, wherein each of said heterocycle may optionally be substituted with up to two substituents independently selected from oxo and C_{1-6}alkyl; or

(f) Q is Ar^2, C_{3-7}cycloalkyl, or C_{1-6}alkyl optionally substituted with Ar^2, hydroxy, C_{1-4}alkoxy, C_{1-4}alkylthio, aminocarbonyl, C_{1-4}alkoxycarbonyl, hydroxy-C_{2-4}-alkyloxy, dioxolanyl substituted with two C_{1-6}alkyl radicals, or a heterocycle selected from pyrrolidinyl, indolyl, imidazolyl, piperidinyl, piperazinyl, and pyridyl, wherein each of said heterocycle may optionally be substituted with up to two substituents independently selected from oxo and C_{1-6}alkyl, and said C_{1-6}alkyl is optionally further substituted with one hydroxy; or

(g) Q is Ar^2, C_{3-7}cycloalkyl, or C_{1-6}alkyl optionally substituted with Ar^2, with one or two hydroxyl groups, with C_{1-4}alkoxy, C_{1-4}alkylthio, aminocarbonyl, C_{1-4}alkoxy-carbonyl, hydroxy-C_{2-4}-alkyloxy, dioxolanyl substituted with two C_{1-6}alkyl radicals, or a heterocycle selected from pyrrolidinyl, indolyl, imidazolyl,

piperidinyl, piperazinyl, and pyridyl, wherein each of said heterocycle may optionally be substituted with two substituents independently selected from oxo and C_{1-6}alkyl; or

(h Q is C_{1-6}alkyl optionally substituted with Ar^2, with one or two hydroxyl groups, with C_{1-4}alkoxy, C_{1-4}alkylthio, aminocarbonyl, C_{1-4}alkoxycarbonyl, or a heterocycle selected from pyrrolidinyl, imidazolyl, piperidinyl and piperazinyl, wherein each of said heterocycle may optionally be substituted with oxo or C_{1-6}alkyl, or with oxo and C_{1-6}alkyl; or

(i) Q is Q is Ar^2.

Interesting subgroups among the subgroups mentioned in the previous paragraph are those wherein Ar^2 is phenyl or phenyl substituted with 1, 2 or 3 substituents or with 1 or 2 substituents, or preferably with one substituent selected from halo, hydroxy, amino, cyano, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxy and aminosulfonyl. Further interesting subgroups among the subgroups mentioned in the previous paragraph are those wherein Ar^2 is phenyl or phenyl substituted with 1, 2 or 3 substituents or with 1 or 2 substituents, or preferably with one substituent selected from amino, cyano, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl and aminosulfonyl.

In particular, Ar^1 is phenyl or phenyl substituted with 1, 2, 3 substituents or with 1, 2 substituents selected from those mentioned in the definition of the compounds of formula (I) or of any subgroup thereof.

Ar^2 is phenyl or phenyl substituted with 1, 2, 3 substituents or with 1, 2 substituents selected from the group consisting of those mentioned in the definition of the compounds of formula (I) or of any subgroup thereof.

In the group of compounds of formula (I) or in any of the subgroups of compounds of formula (I):

(a) Ar^1 preferably is phenyl or phenyl substituted with up to 3 substituents, or with up to 2 substituents, or with one substituent, selected from halo, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, trifluormethyl, and C_{1-6}alkyloxy;

(b) Ar^1 more preferably is phenyl or phenyl substituted with up to 3 substituents, or with up to 2 substituents, or with one substituent, selected from halo, hydroxy, C_{1-6}alkyl and C_{1-6}alkyloxy;

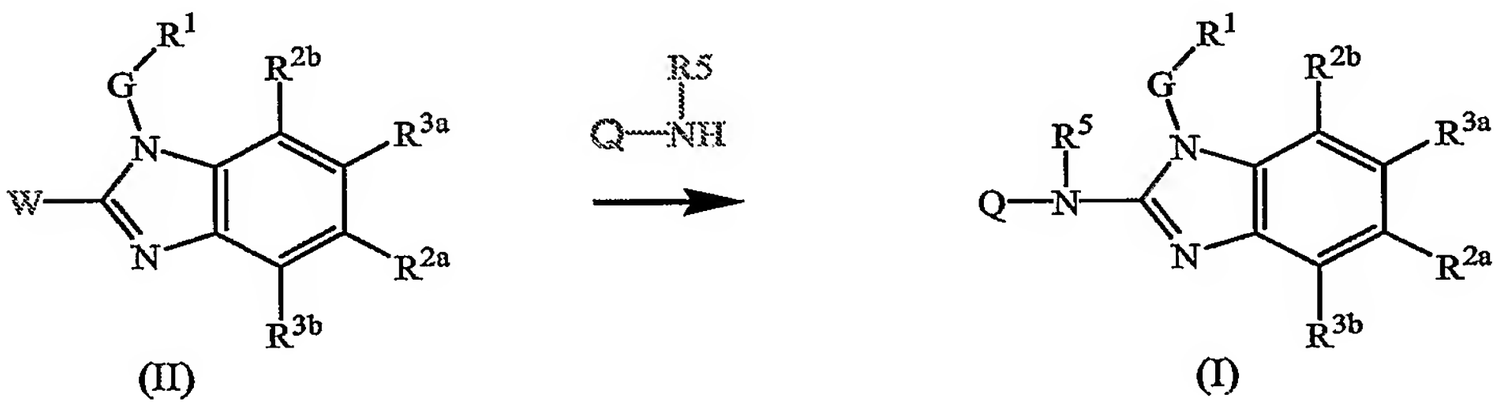
(c) Ar^1 more preferably is phenyl or phenyl substituted with up to 3 substituents, or with up to 2 substituents, or with one substituent, selected from halo and C_{1-6}alkyl.

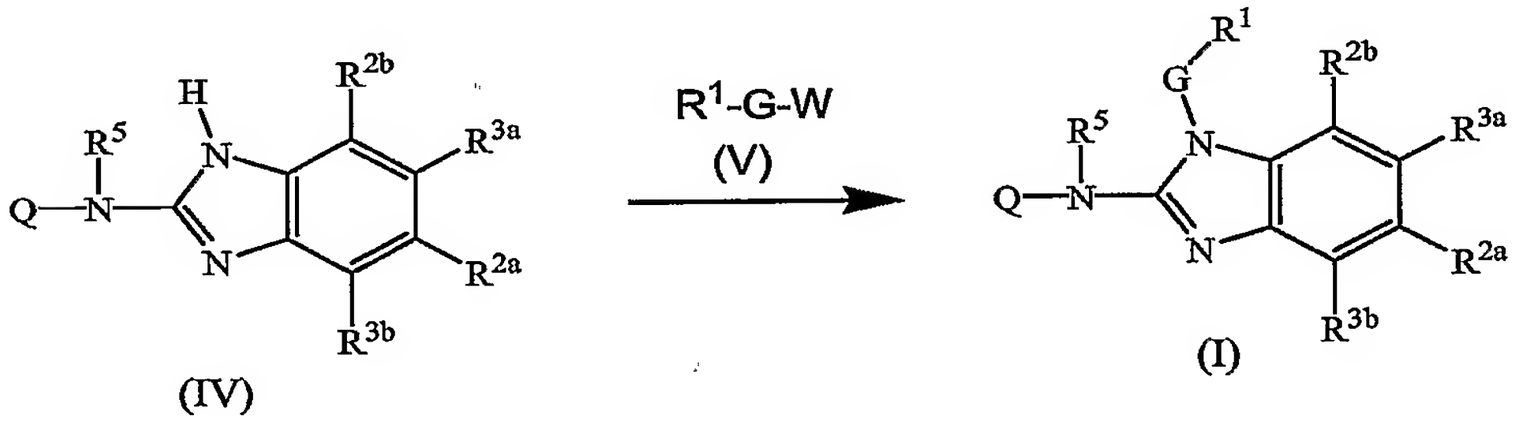
Further particular subgroups of the compounds of formula (I) are those compounds of formula (I), or any subgroup of compounds of formula (I) specified herein, wherein Ar^2 is as defined for Ar^1.

Further particular subgroups of the compounds of formula (I) are those compounds of formula (I), or any subgroup of compounds of formula (I) specified herein, wherein one of R^{2a} and R^{3a} is C_{1-6}alkyl and the other one of R^{2a} and R^{3a} is hydrogen;
in case R^{2a} is different from hydrogen then R^{2b} is C_{1-6}alkyl, and R^{3b} is hydrogen;
in case R^{3a} is different from hydrogen then R^{3b} is C_{1-6}alkyl, and R^{2b} is hydrogen.

Preferred compounds are those compounds listed in tables 1 through 3, more in particular the compound numbers 1 to 11 and 25 to 28.

The compounds of formula (I) or any of the subgroups thereof can be prepared as in the following reaction schemes.





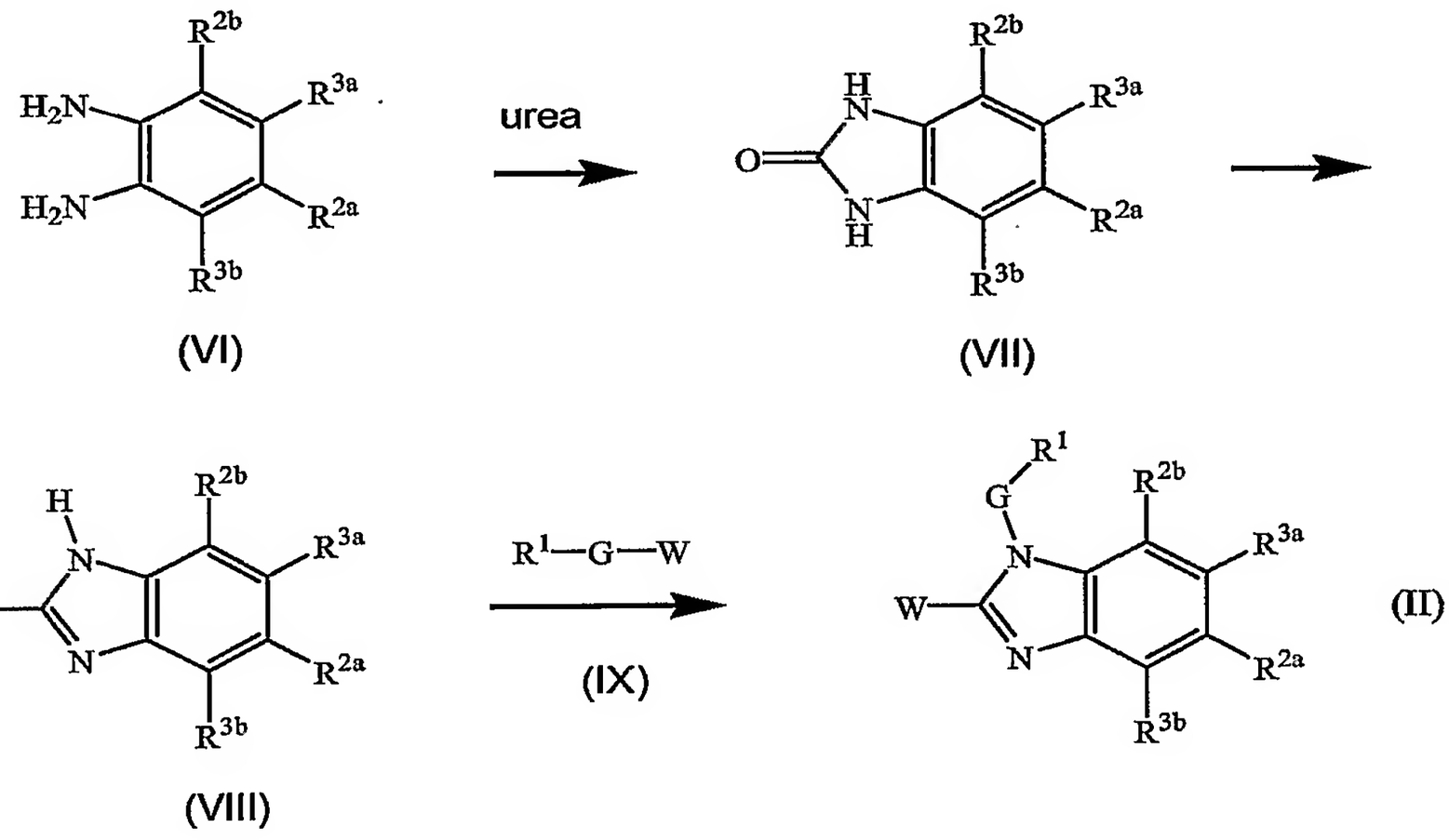
In these schemes Q, G, R^1, R^{2a}, R^{2b} , R^{3a} , R^{3b}, R^5 have the meanings defined above for the compounds of formula (I) or of any of the subgroups thereof. W is an appropriate leaving group, preferably it is chloro or bromo. The reactions of these schemes can be typically conducted in a suitable solvent such as an ether, e.g. THF, a halogenated hydrocarbon, e.g. dichoromethane, $CHCl_3$, toluene, a polar aprotic solvent such as DMF, DMSO, DMA and the like. A base may be added to pick up the acid that is liberated during the reaction. If desired, certain catalysts such as iodide salts (e.g. KI) may be added.

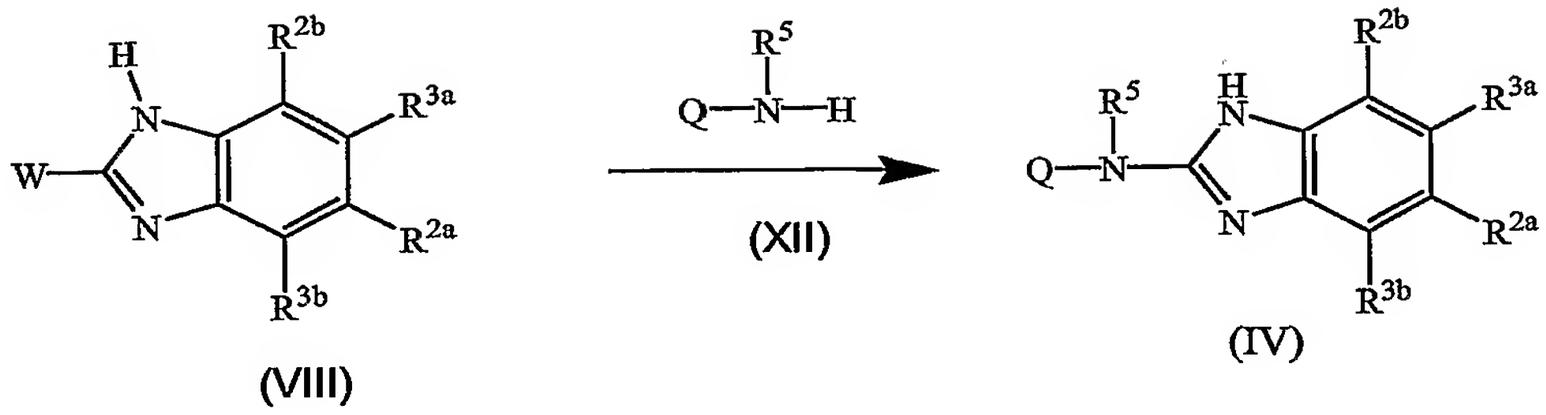
Compounds of formula (I) may be converted into each other following art-known functional group transformation reactions, comprising those described hereinafter. Compounds of formula (I) wherein R^5 is hydrogen may be converted to corresponding compounds of formula (I) wherein is other than hydrogen by an N-alkylation reaction which may be conducted under similar conditions as described above for the conversion of (II) or (IV) to (I).

Compounds wherein Q is C_{1-6}alkyl substituted with C_{1-4}alkoxycarbonyl can be reduced with e.g. $LiAlH_4$ to the corresponding compounds wherein Q is C_{1-6}alkyl substituted with hydroxy. The same starting materials can be reacted with an amine to the corresponding amides.

Compounds of formula (I) wherein Q is Ar having a cyano or a cyanoC_{1-5}alkyl substituent can be reduced with hydrogen in the presence of a suitable catalyst such as Raney nickel, to yield the corresponding methyleneamine or aminoC_{1-6}alkyl substituents.

A number of the intermediates used to prepare the compounds of formula (I) are known compounds or are analogs of known compounds, which can be prepared following modifications of art-known methodologies readily accessible to the skilled person. A number of preparations of intermediates are given hereafter in somewhat more detail. The intermediates of formula (II) and (IV) can be prepared as outlined in the following reaction schemes.





(VIII) (XII) (IV)

In a first step, a diaminobenzene (VI) is cyclized with urea, preferably in a suitable solvent, e.g. xylene, to yield a benzimidazolone (VII). The latter is converted to a benzimidazole derivative (VIII) wherein W is a leaving group as specified above, in particular by reaction of (VII) with a suitable halogenating agent, for example $POCl_3$. The resulting intermediate (VIII) is reacted with an amine derivative (IX) in an N-alkylation reaction to obtain an intermediate (II).

Intermediate (VIII) can be similarly reacted with an amine (XII) to yield intermediate (IV). The above-mentioned reactions are conducted in a suitable solvent and, if desired, in the presence of a base.

The compounds of formula (I) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t.butyl hydro-peroxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g., counter-current distribution, liquid chromatography and the like.

The compounds of formula (I) as prepared in the hereinabove described processes are generally racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) which are sufficiently basic or acidic may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid, respectively chiral base. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali or acid. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

In a further aspect, the present invention concerns a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) as specified herein, or a compound of any of the subgroups of compounds of formula (I) as specified herein, and a pharmaceutically acceptable carrier. A therapeutically effective amount in this context is an amount sufficient to prophylaxictically act against, to stabilize or to reduce viral infection, and in particular RSV viral infection, in infected subjects or subjects being at risk of being infected. In still a further aspect, this invention relates to a process of preparing a pharmaceutical composition as specified herein, which comprises intimately mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a compound of formula (I), as specified herein, or of a compound of any of the subgroups of compounds of formula (I) as specified herein.

Therefore, the compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form or metal complex, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example,

in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin.

The compounds of the present invention may also be administered via oral inhalation or insufflation by means of methods and formulations employed in the art for administration via this way. Thus, in general the compounds of the present invention may be administered to the lungs in the form of a solution, a suspension or a dry powder, a solution being preferred. Any system developed for the delivery of solutions, suspensions or dry powders via oral inhalation or insufflation are suitable for the administration of the present compounds.

Thus, the present invention also provides a pharmaceutical composition adapted for administration by inhalation or insufflation through the mouth comprising a compound of formula (I) and a pharmaceutically acceptable carrier. Preferably, the compounds of the present invention are administered via inhalation of a solution in nebulized or aerosolized doses.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated

to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, suppositories, powder packets, wafers, injectable solutions or suspensions and the like, and segregated multiples thereof.

The compounds of formula (I) show antiviral properties. Viral infections treatable using the compounds and methods of the present invention include those infections brought on by ortho- and paramyxoviruses and in particular by human and bovine respiratory syncytial virus (RSV). A number of the compounds of this invention moreover are active against mutated strains of RSV. Additionally, many of the compounds of this invention show a favorable pharmacokinetic profile and have attractive properties in terms of bioavailabilty, including an acceptable half-life, AUC and peak values and lacking unfavourable phenomena such as insufficient quick onset and tissue retention.

The *in vitro* antiviral activity against RSV of the present compounds was tested in a test as described in the experimental part of the description, and may also be demonstrated in a virus yield reduction assay. The *in vivo* antiviral activity against RSV of the present compounds may be demonstrated in a test model using cotton rats as described in Wyde et al. (Antiviral Research (1998), 38, 31-42).

Due to their antiviral properties, particularly their anti-RSV properties, the compounds of formula (I) or any subgroup thereof, their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms, are useful in the treatment of individuals experiencing a viral infection, particularly a RSV infection, and for the prophylaxis of these infections. In general, the compounds of the present invention may be useful in the treatment of warm-blooded animals infected with viruses, in particular the respiratory syncytial virus.

The compounds of the present invention or any subgroup thereof may therefore be used as medicines. Said use as a medicine or method of treatment comprises the systemic administration to viral infected subjects or to subjects susceptible to viral infections of an amount effective to combat the conditions associated with the viral infection, in particular the RSV infection.

The present invention also relates to the use of the present compounds or any subgroup thereof in the manufacture of a medicament for the treatment or the prevention of viral infections, particularly RSV infection.

The present invention furthermore relates to a method of treating a warm-blooded animal infected by a virus, or being at risk of infection by a virus, in particular by RSV, said method comprising the administration of an anti-virally effective amount of a compound of formula (I), as specified herein, or of a compound of any of the subgroups of compounds of formula (I), as specified herein.

In general it is contemplated that an antiviral effective daily amount would be from 0.01 mg/kg to 500 mg/kg body weight, more preferably from 0.1 mg/kg to 50 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg, and in particular 5 to 200 mg of active ingredient per unit dosage form.

The exact dosage and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight, sex, extent of disorder and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore only guidelines.

Also, the combination of another antiviral agent and a compound of formula (I) can be used as a medicine. Thus, the present invention also relates to a product containing (a) a compound of formula (I), and (b) another antiviral compound, as a combined preparation for simultaneous, separate or sequential use in antiviral treatment. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers. For instance, the compounds of the present invention may be combined with interferon-beta or tumor necrosis factor-alpha in order to treat or prevent RSV infections.

Examples

The following examples are intended to illustrate the present invention and not to limit it thereto. The terms 'compound 1, compound 4, etc. used in these examples refers to the same compounds in the tables.

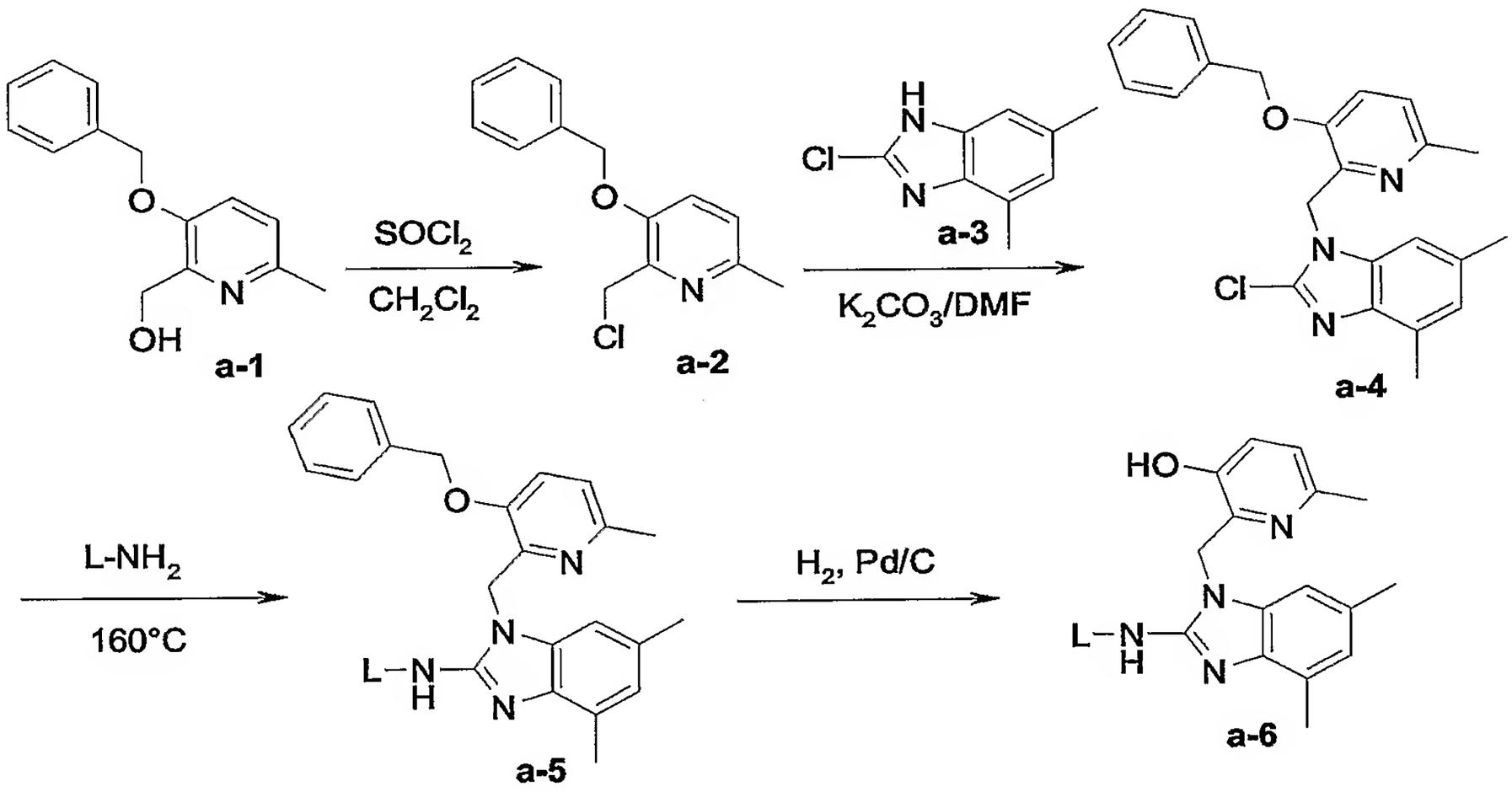
The compounds were identified by LC/MS using the following equipment:

LCT: electrospray ionisation in positive mode, scanning mode from 100 to 900 amu; Xterra MS C18 (Waters, Milford, MA) 5 µm, 3.9 x 150 mm); flow rate 1 ml/min. Two mobile phases (mobile phase A: 85% 6.5mM ammonium acetate + 15% acetonitrile; mobile phase B: 20% 6.5 mM ammonium acetate + 80% acetonitrile) were employed to run a gradient from 100 % A for 3 min to 100% B in 5 min., 100% B for 6 min to 100 % A in 3 min, and equilibrate again with 100 % A for 3 min).

ZQ: electrospray ionisation in both positive and negative (pulsed) mode scanning from 100 to 1000 amu; Xterra RP C18 (Waters, Milford, MA) 5 µm, 3.9 x 150 mm); flow rate 1 ml/min. Two mobile phases (mobile phase A: 85% 6.5mM ammonium acetate + 15% acetonitrile; mobile phase B: 20% 6.5 mM ammonium acetate + 80% acetonitrile) were employed to run a gradient condition from 100 % A for 3 min to 100% B in 5 min., 100% B for 6 min to 100 % A in 3 min, and equilibrate again with 100 % A for 3 min).

Example 1: Preparation of dimethylbenzimidazolamines

Scheme A



Preparation of intermediate ***a-2:***

$SOCl_2$ (14 ml) was added drop wise to a solution of (3-benzyloxy-6-methyl-pyridin-2-yl)-methanol (0.0606 mol) at 5°C. The reaction was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure. The residue was taken up in diethyl ether. The precipitate was filtered off and dried, yielding 16.9g of **a-2** (98%, melting point: 182°C).

*Preparation of intermediate **a-4**:*

A mixture of 2-chloro-4,6-dimethyl-1H-benzimidazole (0.083 mol), **a-2** (0.0913 mol) and K_2CO_3 (0.332 mol) in dimethylformamide (100ml) was stirred at room temperature for 24 hours. H_2O was then added. The mixture was extracted three times with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated at 30°C under reduced pressure. The residue was taken up in CH_3CN/ diisopropylether. The precipitate was filtered off and dried, yielding 16.8g of **a-4** (52%, melting point: 155°C).

*Preparation of intermediate **a-5**:*

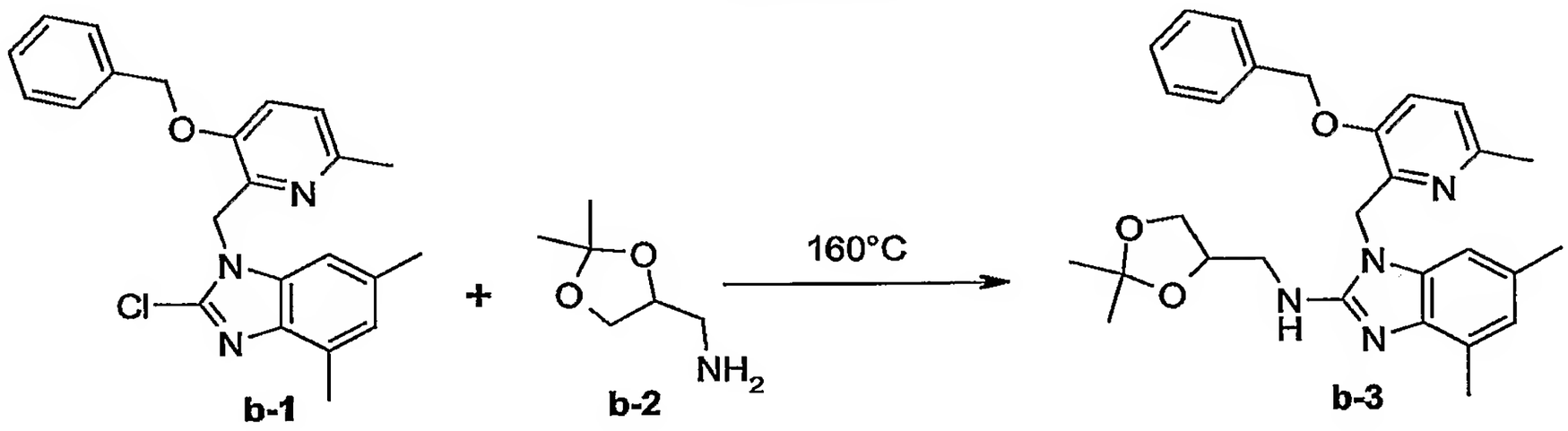
A mixture of **a-4** (0.0007 mol) and 3-piperidin-1-yl-propylamine (0.003 mol) was stirred at 130°C for 2 hours. The residue was crystallized from CH_3CN. The precipitate was filtered off and dried, yielding: 0.174g of [1-(3-benzyloxy-6-methyl-pyridin-2-ylmethyl)-4,6-dimethyl-1H-benzoimidazol-2-yl]-(3-piperidin-1-yl-propyl)-amine (46%).

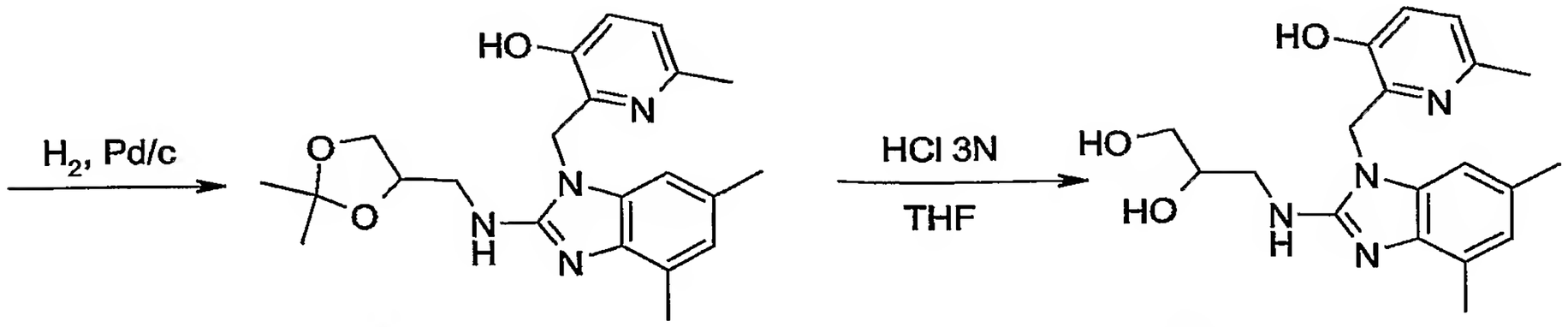
*Preparation of final compound **a-6**:*

A mixture of [1-(3-benzyloxy-6-methyl-pyridin-2-ylmethyl)-4,6-dimethyl-1H-benzoimidazol-2-yl]-(3-piperidin-1-yl-propyl)-amine (0.0003 mol) and Pd/C (0.06g) in CH_3OH (10ml) was hydrogenated at room temperature for 1 hour under a 3 bar pressure, then filtered over celite. The filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 89/10/1; 10µm). The pure fractions were collected and the solvent was evaporated. The residue (0.084g) was crystallized from CH_3CN. The precipitate was filtered off and dried, yielding 0.073g of 2-[4,6-dimethyl-2-(3-piperidin-1-yl-propylamino)-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol (Compound 1, 51%, melting point: > 260°C).

Example 2: Preparation of dihydroxyalkyl substituted dimethylbenzimidazoleamines

Scheme B





b-4 **b-5**

*Preparation of intermediate **b-3**:*

A mixture of **b-1** (0.0014 mol) and **b-2** (0.0012 mol) was stirred at 130°C for 3 hours, then stirred at 160°C for 2 hours, cooled down to room temperature and taken up in CH_2Cl_2. The organic layer was washed with a 10% solution of K_2CO_3, dried (over $MgSO_4$), filtered and the solvent was evaporated until dryness. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 97/3/0.1). The pure fractions were collected and the solvent was evaporated, yielding 0.55g of intermediate **b-3** (81%).

*Preparation of compound **b-4**:*

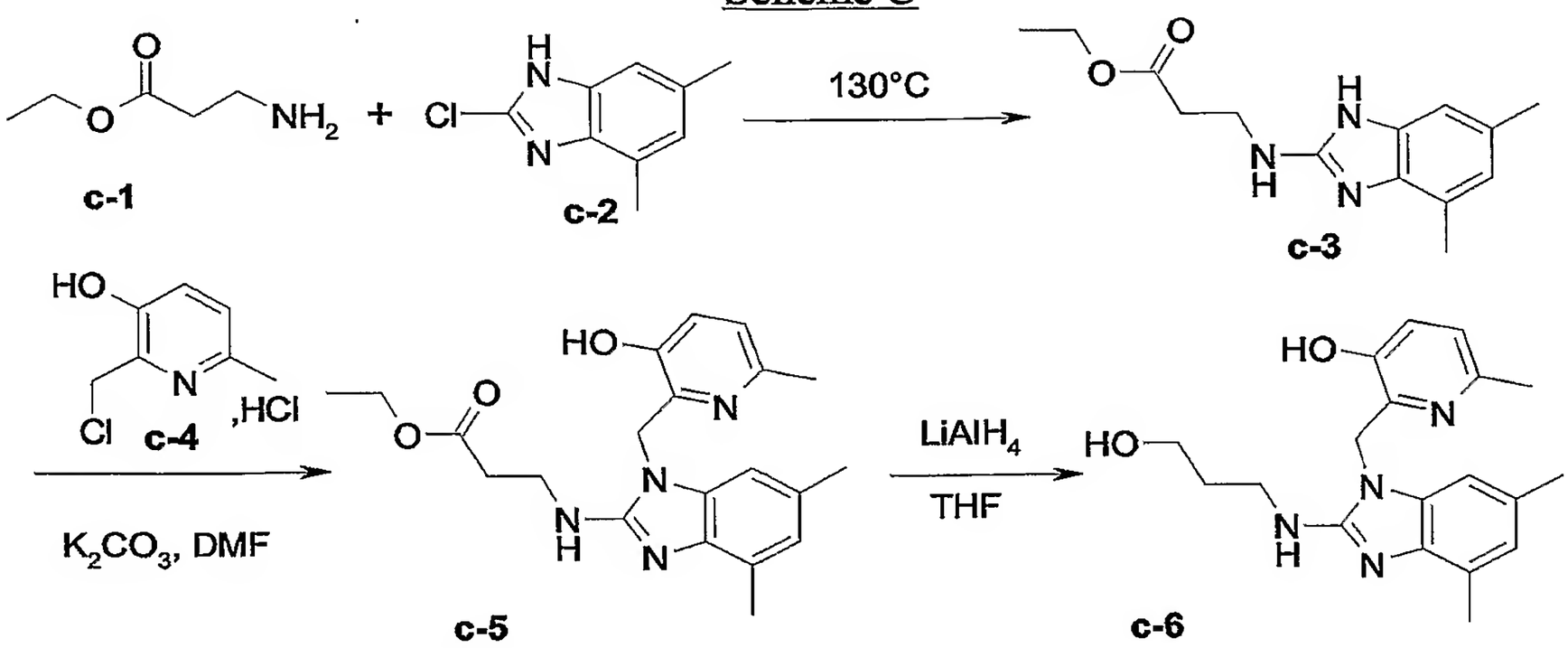
A mixture of **b-3** (0.0011 mol) and Pd/C (0.18g) in CH_3OH (10ml) was hydrogenated for 1 hour under a 3 bar pressure, then filtered over celite. Celite was rinsed with CH_3OH. The filtrate was concentrated under reduced pressure. The residue (0.47g) was crystallized from CH_3CN. The precipitate was filtered off and dried, yielding 0.27g of 2-{2-[(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-amino]-4,6-dimethyl-benzoimidazol-1-ylmethyl}-6-methyl-pyridin-3-ol (compound 21, 60%, melting point: 225°C).

*Preparation of final compound **b-5**:*

A mixture of 2-{2-[(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-amino]-4,6-dimethyl-benzoimidazol-1-ylmethyl}-6-methyl-pyridin-3-ol (0.0005 mol) in a 3N solution of HCl (15ml) and tetrahydrofuran (15ml) was stirred for 4 hours. Tetrahydrofuran was evaporated under reduced pressure. The mixture was basified with K_2CO_3 (powder). The aqueous layer was saturated with K_2CO_3 (powder). A solution of CH_2Cl_2/CH_3OH (90/10) was added. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated. The residue (0.17g, 88%) was crystallized from CH_3CN/ diisopropylether. The precipitate was filtered off and dried. Yielding: 0.085g of 3-[1-(3-hydroxy-6-methyl-pyridin-2-ylmethyl)-4,6-dimethyl-1H-benzoimidazol-2-ylamino]-propane-1,2-diol (compound 4, melting point: 205°C).

Example 3: Preparation of hydroxyalkyl substituted dimethylbenzimidazoleamines

Scheme C



Preparation of intermediate c-3:

A mixture of **c-2** (0.004 mol) and **c-1** (0.006 mol) was stirred at 130°C for 12 hours, and then taken up in CH_2Cl_2. The organic layer was washed with a 10% solution of K_2CO_3, dried (over $MgSO_4$), filtered and the solvent was evaporated until dryness. The residue (0.6g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 95/5/0.2; 10µm). The pure fractions were collected and the solvent was evaporated, yielding 0.4g of intermediate **c-3** (38%).

Preparation ofcompound c-5:

A mixture of **c-3** (0.0015 mol), **c-4** (0.0016 mol) and K_2CO_3 (0.0052 mol) in dimethyl-formamide (20ml) was stirred at 70°C for 4 hours. The solvent was evaporated until dryness. The residue was taken up in CH_2Cl_2. The organic layer was washed with H_2O, dried (over $MgSO_4$), filtered and the solvent was evaporated. The residue (0.81g) was purified by column chromatography over silica gel (eluent: toluene/2-propanol/NH_4OH 90/10/0.5; 10µm). The pure fractions were collected and the solvent was evaporated. The residue (0.12g) was crystallized from 2-propanol/CH_3CN/diisopropylether. The precipitate was filtered off and dried, yielding 0.12g of 3-[1-(3-hydroxy-6-methyl-pyridin-2-ylmethyl)-4,6-dimethyl-1H-benzoimidazol-2-ylamino]-propionic acid ethyl ester (compound 12, 21%, melting point: 180°C).

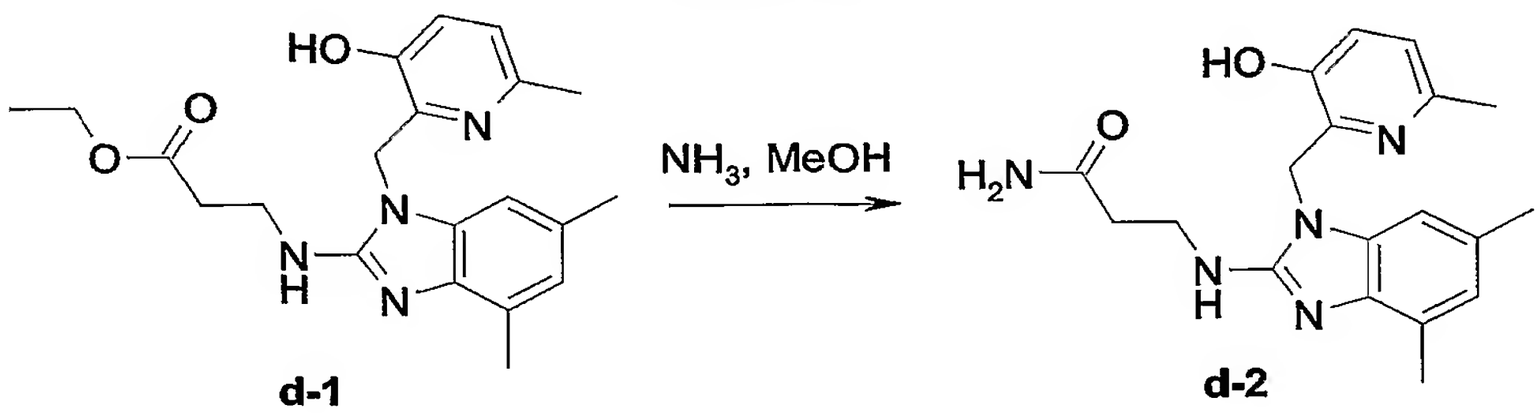
Preparation of final compound c-6:

$LiAlH_4$ (0.0003 mol) was added portion wise at 5°C to a mixture of 3-[1-(3-hydroxy-6-methyl-pyridin-2-ylmethyl)-4,6-dimethyl-1H-benzoimidazol-2-ylamino]-propionic acid ethyl ester (0.0001 mol) in tetrahydrofuran (10ml) under N_2 flow. The mixture was stirred at 5°C for 1 hour, then at room temperature for 3 hours. Ethylacetate and H_2O were added. The mixture was extracted with ethylacetate. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated until dryness. The residue was crystallized from 2-propanone/CH_3CN/ diisopropylether. The

precipitate was filtered off and dried, yielding 0.025g of 2-[2-(3-hydroxypropylamino)-4,6-dimethyl-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol (compound 7, 73%, melting point: 170°C).

Example 4: Preparation of amidoalkyl substituted dimethylbenzimidazoleamines

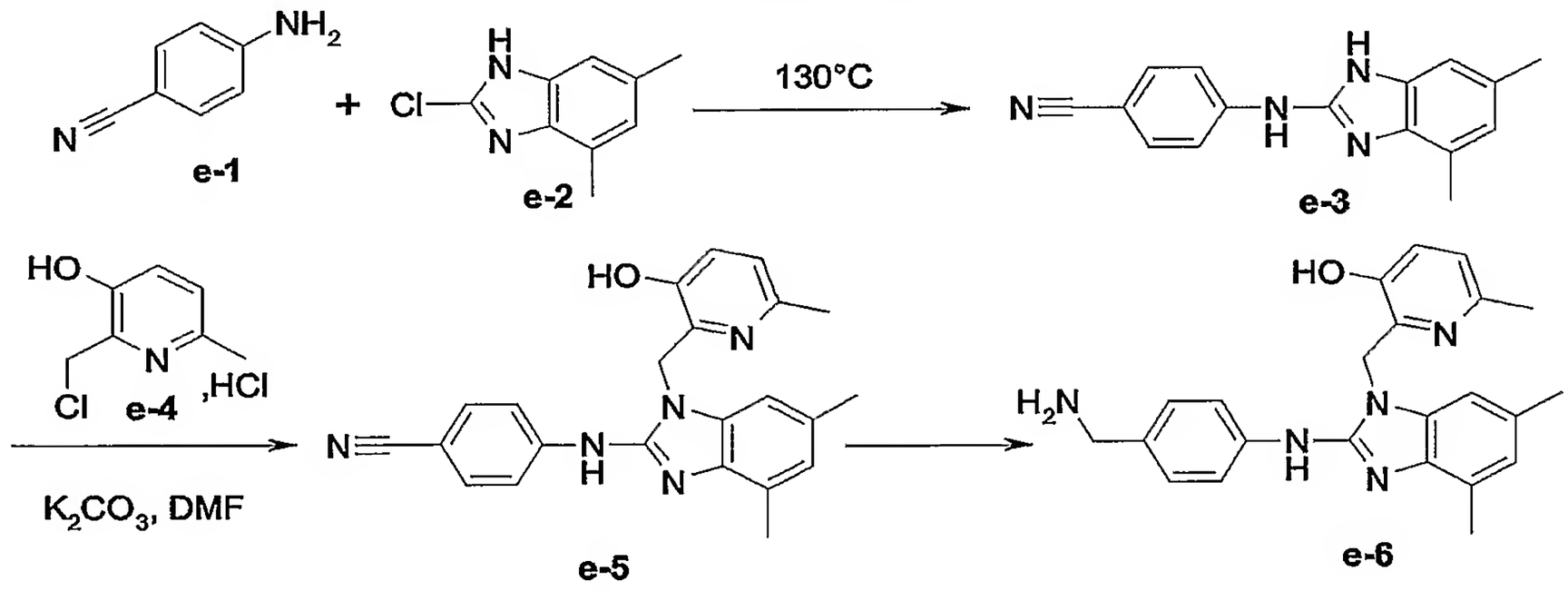
Scheme D



A mixture of 3-[1-(3-hydroxy-6-methyl-pyridin-2-ylmethyl)-4,6-dimethyl-1H-benzoimidazol-2-ylamino]-propionic acid ethyl ester (0.0001 mol) in a saturated solution of NH_3 in CH_3OH (10ml) was stirred at 70°C for 6 hours. The solvent was evaporated until dryness. The residue (0.05g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 88/12/1; 10µm). The pure fractions were collected and the solvent was evaporated. The residue (0.022g, 48%) was crystallized from 2-propanone/CH_3CN/diisopropylether. The precipitate was filtered off and dried, yielding 0.014g of 3-[1-(3-hydroxy-6-methyl-pyridin-2-ylmethyl)-4,6-dimethyl-1H-benzoimidazol-2-ylamino]-propionamide **d-2** (compound 8, 30%, melting point: 229°C).

Example 5: Preparation of aryl substituted dimethylbenzimidazoleamines

Scheme E



Preparation of intermediate **e-3:**

A mixture of **e-1** (0.0022 mol) and **e-2** (0.0023 mol) was stirred at 130°C for 1 hour, then cooled down to room temperature and taken up in CH_2Cl_2. The precipitate was

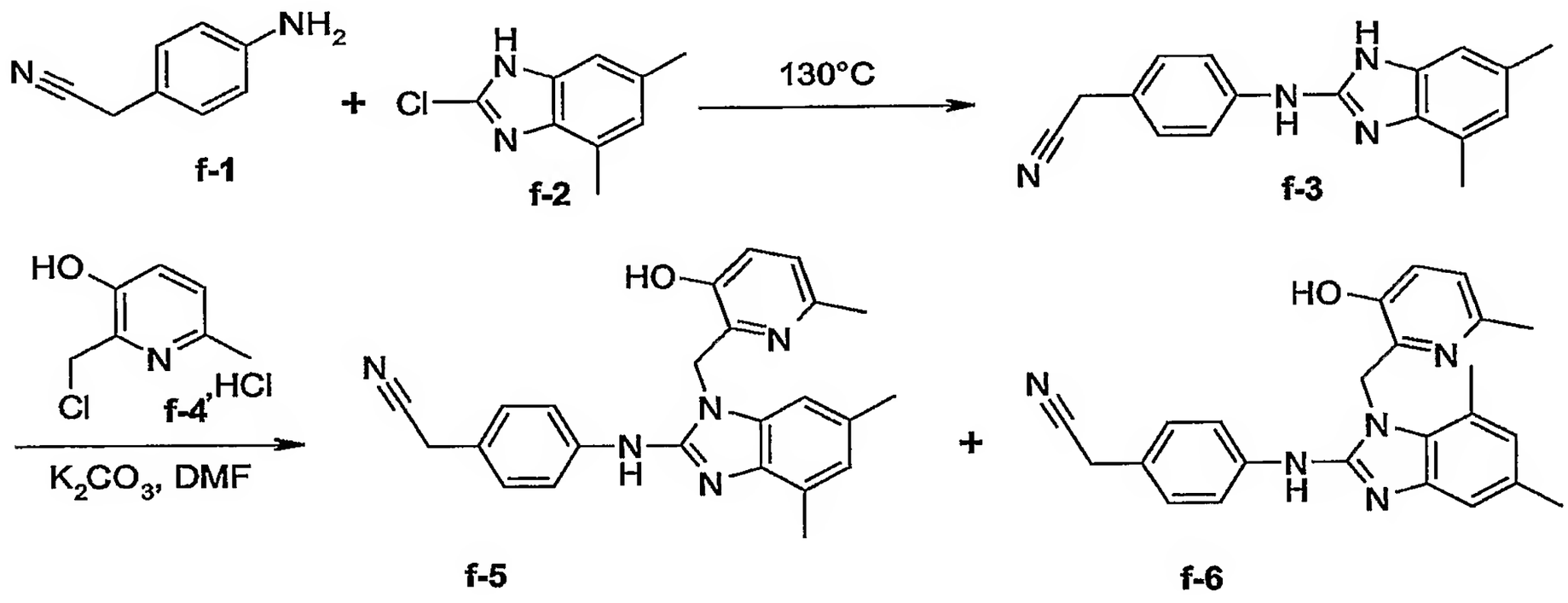
filtered. The mother layer was evaporated. The residue (0.522g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 99/1/0.1 to 90/10/1; 5µm). The pure fractions were collected and the solvent was evaporated, yielding 0.36g of intermediate **e-3** (62%).

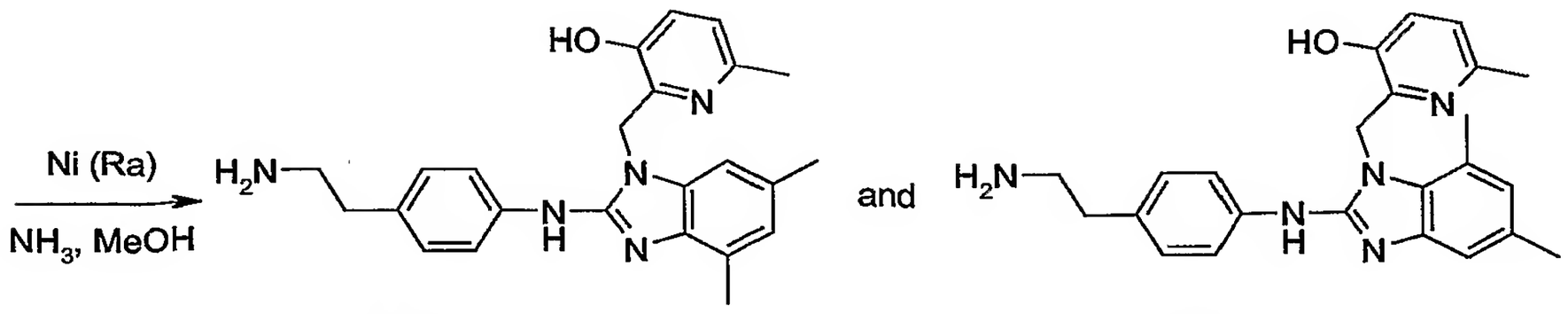
Preparation ofcompound **e-5:**
4-[1-(3-Hydroxy-6-methyl-pyridin-2-ylmethyl)-4,6-dimethyl-1H-benzoimidazol-2-ylamino]-benzonitrile (compound 20, melting point: > 260°C) was prepared analogous to the procedure described for **c-5**.

Preparation of final compound e-6:
Raney Nickel (0.2g) was added to a mixture of **e-5** (0.0001 mol) in a saturated solution of NH_3 in CH_3OH (20ml). The mixture was hydrogenated at room temperature for 3 hours under a 5 bar pressure, then filtered over celite. Celite was rinsed with H_2O. The filtrate was evaporated until dryness. The residue (0.07g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 85/15/1; 10µm). The pure fractions were collected and the solvent was evaporated. The residue (0.042g, 84%) was crystallized from 2-propanone/CH_3CN/diisopropylether. The precipitate was filtered off and dried, yielding 0.022g of 2-[2-(4-aminomethyl-phenylamino)-4,6-dimethyl-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol, **e-6** (compound 9, 44%, melting point: 255°C).

Example 6: Preparation of aryl substituted dimethylbenzimidazoleamines

Scheme F





Preparation of intermediate f-3:

The intermediate **f-3** was prepared analogous to the procedure described for intermediate **e-3**.

Preparation of intermediates f-5 and f-6:

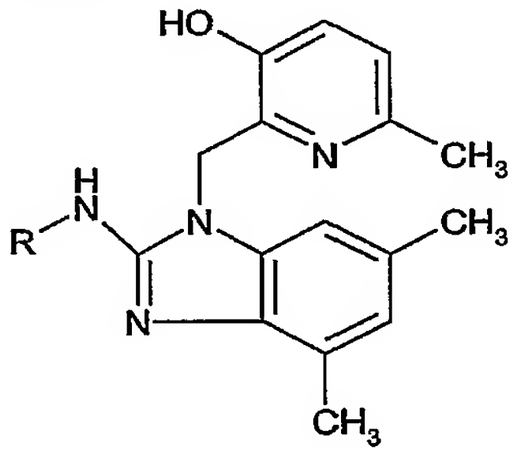
The mixture of intermediates **f-5** and **f-6** has been prepared analogous to the procedure described for **c-5**.

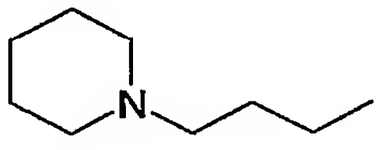
Preparation of f-7 and f-8:

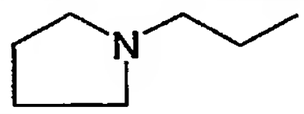
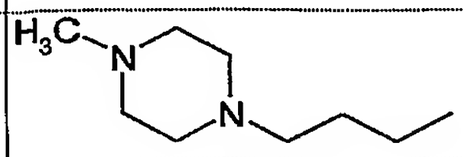
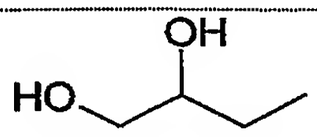
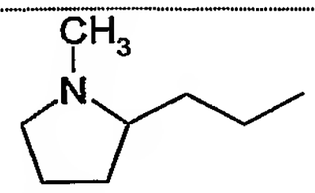
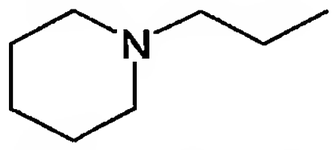
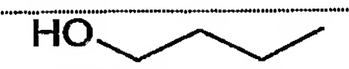
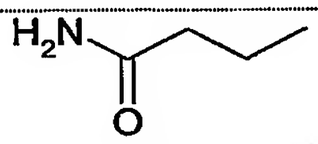
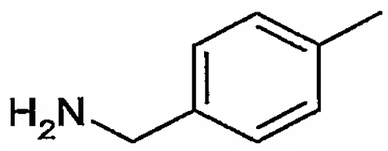
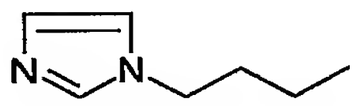
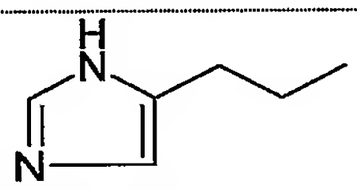
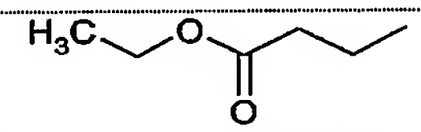
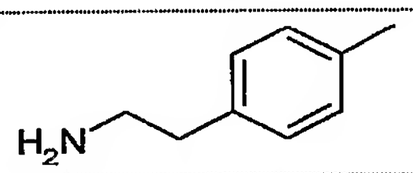
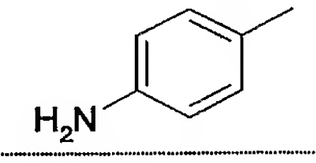
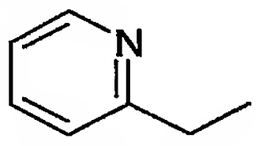
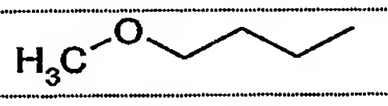
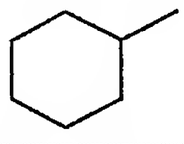
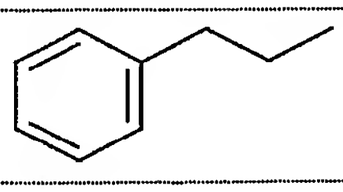
The compounds **f-7** and **f-8** have been prepared analogous to the procedure described for **e-6,** yielding 0.18g of fraction 1 (10%) and 0.36g of fraction 2 (20%). Fraction 1 was transformed in acetate and crystallized from 2-propanone/CH_3CN/diisopropylether. The precipitate was filtered off and dried, yielding 0.013g of **f-8** (7.5%, 1 CH_3CO_2H, melting point: 171°C). Fraction 2 was dissolved in 2-propanol/HCl and converted into the hydrochloric acid salt. The precipitate was filtered off and dried. The residue was crystallized from 2-propanol/diisopropylether. The precipitate was filtered off and dried, yielding 0.021g of **f-7** (compound 26, 10.4%, 4 HCl, melting point: 213°C).

The following tables list compounds of the present invention that were prepared analogous to any one of the above mentioned synthesis schemes.

Table 1



Comp. No.	R	Activity	Mass Spectroscopy	Melting point	Synthesis Scheme / salt form
1		*7.7*	$MH^+ = 408$	> 260°C	A

Comp. No.	R	Activity	Mass Spectroscopy	Melting point	Synthesis Scheme / salt form
2		*7.7*	$MH^+ = 394$	225°C	A
3		*7.6*	$MH^+ = 423$	225°C	A
4		*7.4*	$MH^+ = 357$	205°C	B
5		*7.4*	$MH^+ = 394$	185°C	A
6		*7.2*	$MH^+ = 394$	230°C	A
7		*6.8*	$MH^+ = 341$	170°C	C
8		*6.8*	$MH^+ = 354$	229°C	D
9		*6.6*	$MH^+ = 388$	255°C	E
10		*6.3*	$MH^+ = 391$	255°C	A
11		*6.2*	$MH^+ = 377$	> 260°C	A
12		*5.5*	$MH^+ = 383$	180°C	C
13		*5.5*	$MH^+ = 402$	171°C	F / HCl
14		*4.0*	$MH^+ = 374$	254°C	E
15		*5.8*	$MH^+ = 374$	208°C	C
16		*4.0*	$MH^+ = 355$	206°C	C
17		*4.0*	$MH^+ = 365$	176°C	F
18		*4.0*	$MH^+ = 387$	232°C	C

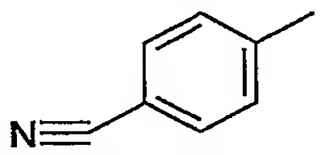
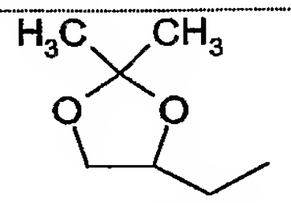
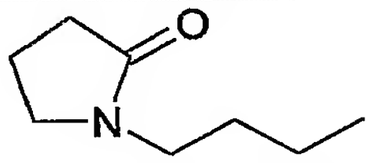
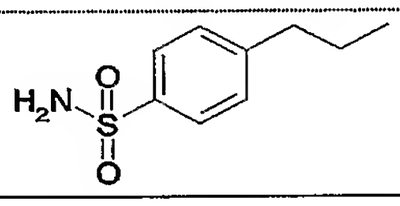
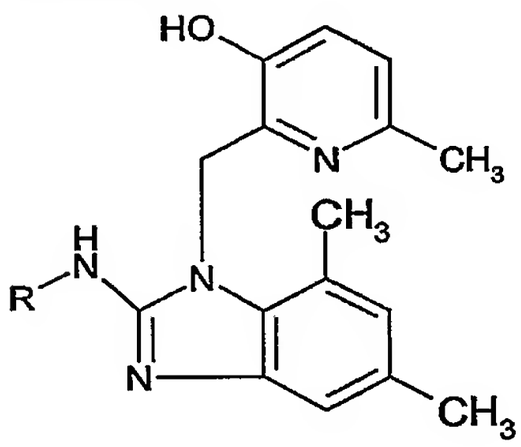
Comp. No.	R	Activity	Mass Spectroscopy	Melting point	Synthesis Scheme / salt form
19		*4.0*	$MH^+ = 384$	> 260°C	E
20		*4.0*	$MH^+ = 397$	225°C	B
21		*4.0*	$MH^+ = 408$	170°C	A
22		*4.2*	$MH^+ = 466$	> 260°C	A

Table 2



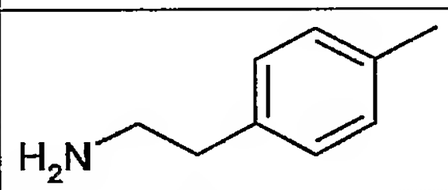
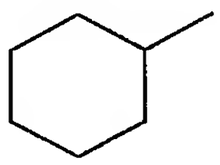
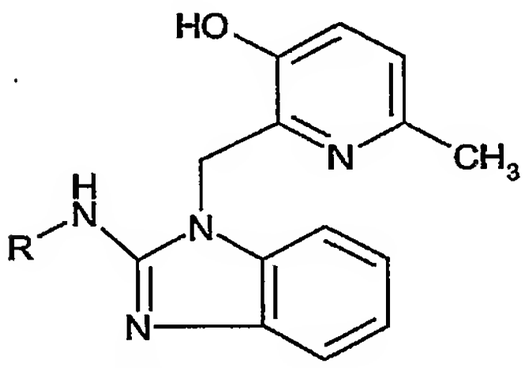
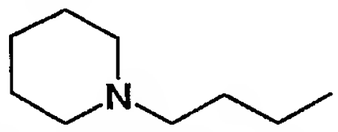
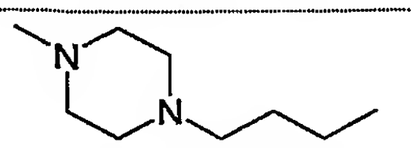
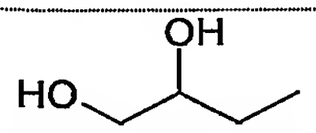
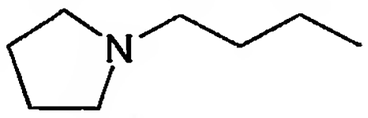
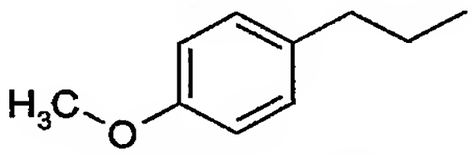
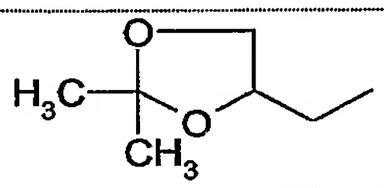
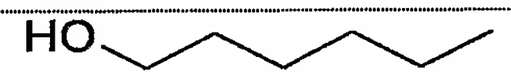
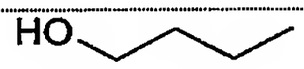
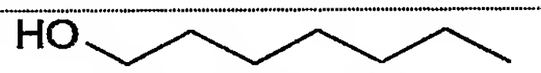
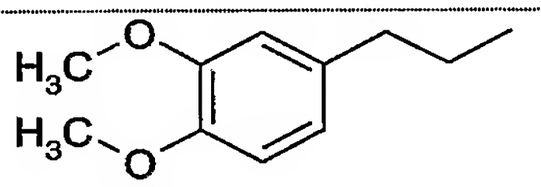
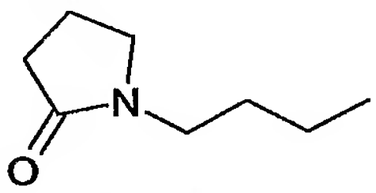
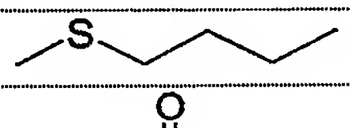
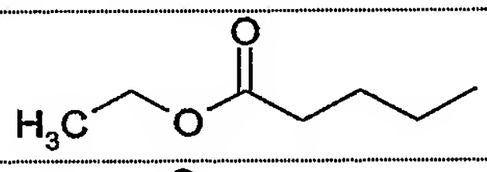
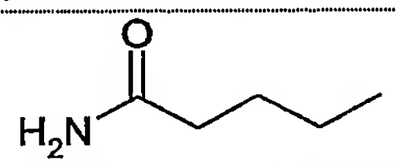
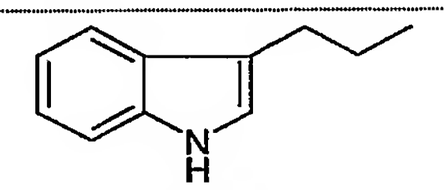
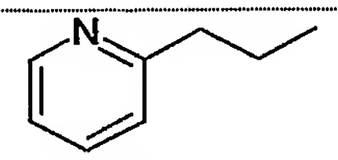
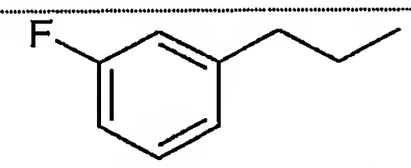
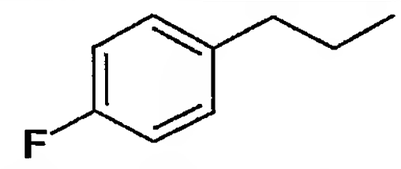
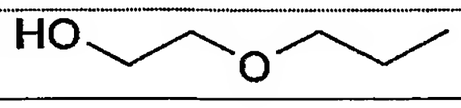
Comp. No.	R	Activity	Mass Spectroscopy	Melting point	Synthesis scheme / salt form
23		*5.2*	$MH^+ = 402$	171°C	F / acetate
24		*4.0*	$MH^+ = 379$	222°C	F

Table 3



Comp. No.	R	Activity	Mass Spectroscopy	Melting point	Synthesis scheme

Comp. No.	R	Activity	Mass Spectroscopy	Melting point	Synthesis scheme
25		*6.5*	$MH^+ = 380$	195°C	C
26		*6.5*	$MH^+ = 395$	190°C	C
27		*6.3*	$MH^+ = 329$	170°C	C
28		*6.2*	$MH^+ = 366$	190°C	C
29		*5.6*	$MH^+ = 389$	215°C	C
30		*5.4*	$MH^+ = 369$	221°C	C
31		*5.3*	$MH^+ = 341$	182°C	C
32		*5.0*	$MH^+ = 313$	210°C	C
33		*5.0*	$MH^+ = 355$	185°C	C
34		*5.0*	$MH^+ = 419$	180°C	C
35		*4.9*	$MH^+ = 380$	175°C	C
36		*4.8*	$MH^+ = 343$	205°C	C
37		*4.0*	$MH^+ = 369$	215°C	C
38		*4.3*	$MH^+ = 340$	220°C	C
39		*4.0*	$MH^+ = 398$	245°C	C
40		*4.3*	$MH^+ = 360$	225°C	C
41		*4.0*	$MH^+ = 377$	245°C	C

Comp. No.	R	Activity	Mass Spectroscopy	Melting point	Synthesis scheme
42		*4.0*	$MH^+ = 377$	250°C	C
43		*4.1*	$MH^+ = 343$	215°C	C

Example 7*: **In vitro screening for activity against Respiratory Syncytial Virus.***

The percent protection against cytopathology caused by viruses (antiviral activity or EC_{50}) achieved by tested compounds and their cytotoxicity (CC_{50}) are both calculated from dose-response curves. The selectivity of the antiviral effect is represented by the selectivity index (SI), calculated by dividing the CC_{50} (cytotoxic dose for 50% of the cells) by the EC_{50} (antiviral activity for 50 % of the cells). The tables in the above experimental part list the category to which each of the prepared compounds belong : Compounds belonging to activity category "A" have an pEC_{50} (-log of EC_{50} when expressed in molar units) equal to or more than 6. Compounds belonging to activity category "B" have a pEC50 value below 6.

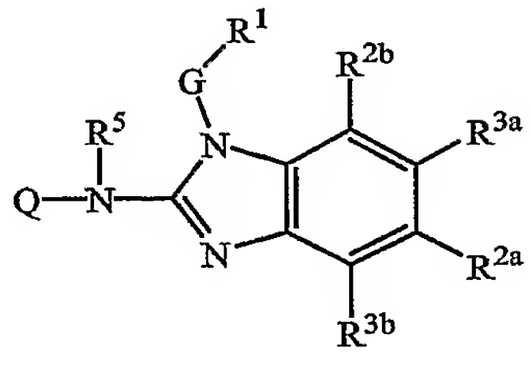
Automated tetrazolium-based colorimetric assays were used for determination of EC_{50} and CC_{50} of test compounds. Flat-bottom, 96-well plastic microtiter trays were filled with 180 µl of Eagle's Basal Medium, supplemented with 5 % FCS (0% for FLU) and 20 mM Hepes buffer. Subsequently, stock solutions (7.8 x final test concentration) of compounds were added in 45 µl volumes to a series of triplicate wells so as to allow simultaneous evaluation of their effects on virus- and mock-infected cells. Five five-fold dilutions were made directly in the microtiter trays using a robot system. Untreated virus controls, and HeLa cell controls were included in each test. Approximately 100 $TCID_{50}$ of Respiratory Syncytial Virus was added to two of the three rows in a volume of 50 µl. The same volume of medium was added to the third row to measure the cytotoxicity of the compounds at the same concentrations as those used to measure the antiviral activity. After two hours of incubation, a suspension (4×10^5 cells/ml) of HeLa cells was added to all wells in a volume of 50µl. The cultures were incubated at 37°C in a 5% CO_2 atmosphere. Seven days after infection the cytotoxicity and the antiviral activity was examined spectrophotometrically. To each well of the microtiter tray, 25 µl of a solution of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was added . The trays were further incubated at 37°C for 2 hours, after which the medium was removed from each cup. Solubilization of the formazan crystals was achieved by adding 100 µl 2-propanol. Complete dissolution of the formazan crystals were obtained after the trays have been placed on a plate shaker for 10 min. Finally, the

absorbances were read in an eight-channel computer-controlled photometer (Multiskan MCC, Flow Laboratories) at two wavelengths (540 and 690 nm). The absorbance measured at 690 nm was automatically subtracted from the absorbance at 540 nm, so as to eliminate the effects of non-specific absorption.

5

Claims

1. A compound of formula (I)



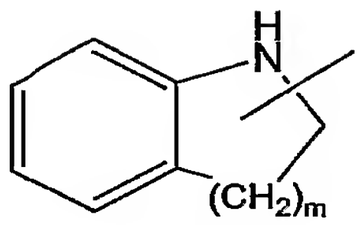
(I)

a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex or stereochemically isomeric form thereof, wherein

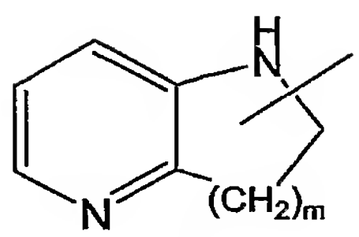
Q is Ar^2, C_{3-7}cycloalkyl, or C_{1-6}alkyl substituted with one or more substituents each independently selected from the group consisting of trifluoromethyl, C_{3-7}cycloalkyl, Ar^2, hydroxy, C_{1-4}alkoxy, C_{1-4}alkylthio, Ar^2-oxy-, Ar^2-thio-, $Ar^2(CH_2)_n$oxy, $Ar^2(CH_2)_n$thio, hydroxycarbonyl, aminocarbonyl, C_{1-4}alkylcarbonyl, Ar^2carbonyl, C_{1-4}alkoxycarbonyl, $Ar^2(CH_2)_n$carbonyl, aminocarbonyloxy, C_{1-4}alkylcarbonyloxy, Ar^2carbonyloxy, $Ar^2(CH_2)_n$carbonyloxy, hydroxy-C_{2-4}-alkyloxy, C_{1-4}alkoxycarbonyl$(CH_2)_n$oxy, mono- or di(C_{1-4}alkyl)aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyloxy, aminosulfonyl, mono- or di(C_{1-4}alkyl)aminosulfonyl, dioxolanyl optionally substituted with one or two C_{1-6}alkyl radicals, and a heterocycle selected from the group consisting of pyrrolidinyl, pyrrolyl, dihydropyrrolyl, indolyl, imidazolyl, triazolyl, piperidinyl, homopiperidinyl, piperazinyl, pyridyl and tetrahydropyridyl, wherein each of said heterocycle may optionally be substituted with oxo or C_{1-6}alkyl;

G is a direct bond or C_{1-10}alkanediyl optionally substituted with one or more substituents individually selected from the group consisting of hydroxy, C_{1-6}alkyloxy, Ar^1C_{1-6}alkyloxy, C_{1-6}alkylthio, Ar^1C_{1-6}alkylthio, $HO(-CH_2-CH_2-O)_n$-, C_{1-6}alkyloxy$(-CH_2-CH_2-O)_n$- and Ar^1C_{1-6}alkyloxy$(-CH_2-CH_2-O)_n$-;

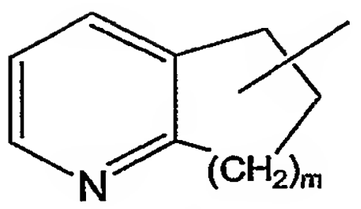
R^1 is Ar^1 or a monocyclic or bicyclic heterocycle being selected from piperidinyl, piperazinyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, tetrahydrofuranyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, isothiazolyl, pyrazolyl, isoxazolyl, oxadiazolyl, quinolinyl, quinoxalinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, pyridopyridyl, naphthiridinyl, 1*H*-imidazo[4,5-b]pyridinyl, 3*H*-imidazo[4,5-b]pyridinyl, imidazo[1,2-a]-pyridinyl, 2,3-dihydro-1,4-dioxino[2,3-b]pyridyl and a radical of formula



(c-1)



(c-2)



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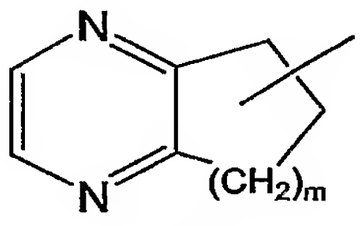

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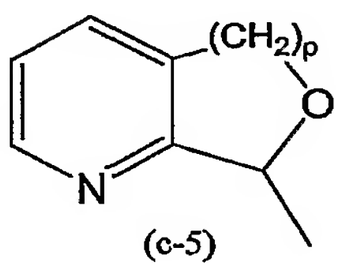

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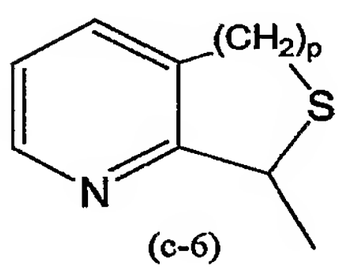
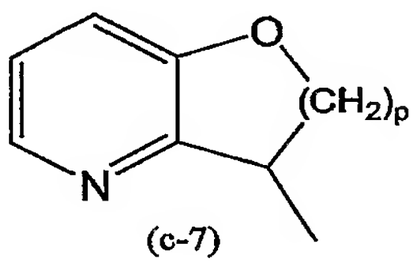
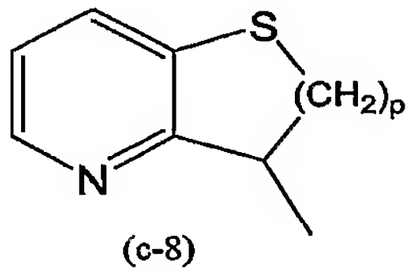


(c-6)



(c-7)



(c-8)

;

wherein each of said monocyclic or bicyclic heterocycles may optionally be substituted with 1 or where possible more, such as 2, 3, 4 or 5, substituents individually selected from the group of substituents consisting of halo, hydroxy, amino, cyano, carboxyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, Ar^1, Ar^1C_{1-6}alkyl, Ar^1C_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{4a}-, Ar^1-SO_2-NR^{4a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{4a}R^{4b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, Ar^1C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-;

each n independently is 1, 2, 3 or 4;

one of R^{2a} and R^{3a} is C_{1-6}alkyl and the other one of R^{2a} and R^{3a} is hydrogen;

in case R^{2a} is different from hydrogen then R^{2b} is hydrogen or C_{1-6}alkyl, and R^{3b} is hydrogen;

in case R^{3a} is different from hydrogen then R^{3b} is hydrogen or C_{1-6}alkyl, and R^{2b} is hydrogen; or

R^{2a}, R^{2b}, R^{3a} and R^{3b} all are hydrogen;

R^{4a} and R^{4b} can be the same or can be different relative to one another, and are each independently hydrogen or C_{1-6}alkyl; or

R^{4a} and R^{4b} taken together may form a bivalent radical of formula -(CH_2)$_s$-;

R^5 is hydrogen or C_{1-6}alkyl;

m is 1 or 2;

p is 1 or 2;

s is 4 or 5

Ar^1 is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, and C_{1-6}alkyloxy;

Ar^2 is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from the group consisting of halo, hydroxy, amino, cyano, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxy, aminosulfonyl, aminocarbonyl, hydroxycarbonyl, C_{1-4}alkylcarbonyl, mono- or di(C_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyl)aminocarbonyl, mono- or di(C_{1-4}alkyl)aminosulfonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl and C_{1-4}alkoxycarbonyl.

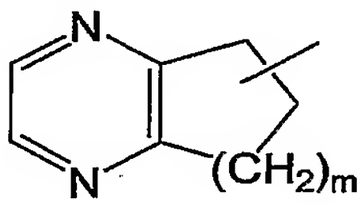
2. A compound according to claim 1 wherein G is C_{1-10}alkanediyl.

3. A compound according to claim 1, wherein G is methylene.

4. A compound according to any of claims 1 - 3, wherein R^1 is pyridyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of halo, hydroxy, amino, cyano, carboxyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, Ar^1, Ar^1C_{1-6}alkyl, Ar^1C_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)amino-C_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{4a}-, Ar^1-SO_2-NR^{4a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{4a}R^{4b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, Ar^1C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-.

5. A compound according to any of claims 1 - 3, wherein R^1 is pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of hydroxy and C_{1-6}alkyl.

6. A compound according to any of claims 1 - 3, wherein R^1 is Ar^1, quinolinyl, benzimidazolyl, a radical of formula



(c-4)

or pyrazinyl; wherein each of the radicals Ar^1, quinolinyl, benzimidazolyl, (c-4), or pyrazinyl may optionally be substituted with the substitutents of said radicals as claimed in claim1.

7. A compound according to any of claims 1 - 3, wherein R^1 is phenyl optionally substituted with one, two or three radicals selected from the group consisting of halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy; quinolinyl; a radical (c-4) wherein m is 2, optionally substituted with up to two radicals selected from C_{1-6}alkyl; benzimidazolyl optionally substituted with C_{1-6}alkyl; pyrazinyl optionally substituted with up to three radicals selected from C_{1-6}alkyl.

8. A compound according to any of claims 1 - 7, wherein R^5 is hydrogen.

9. A compound according to any of claims 1 - 8, wherein Q is Ar^2, C_{3-7}cycloalkyl, or C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from the group consisting of trifluoromethyl, Ar^2, hydroxy, C_{1-4}alkoxy, C_{1-4}alkylthio, Ar^2-oxy-, $Ar^2(CH_2)_n$oxy, hydroxycarbonyl, aminocarbonyl, C_{1-4}alkylcarbonyl, Ar^2carbonyl, C_{1-4}alkoxycarbonyl, C_{1-4}alkylcarbonyloxy, hydroxy-C_{2-4}-alkyloxy, mono- or di(C_{1-4}alkyl)-aminocarbonyl, dioxolanyl optionally substituted with one or two C_{1-6}alkyl radicals, and a heterocycle selected from the group consisting of pyrrolidinyl, pyrrolyl, dihydropyrrolyl, indolyl, imidazolyl, triazolyl, piperidinyl, homopiperidinyl, piperazinyl, pyridyl and tetrahydropyridyl, wherein each of said heterocycle may optionally be substituted with up to two substituents independently selected from oxo and C_{1-6}alkyl.

10. A compound according to any of claims 1 - 8, wherein Q is Ar^2, C_{3-7}cycloalkyl, or C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from the group consisting of Ar^2, hydroxy, C_{1-4}alkoxy, C_{1-4}alkylthio, aminocarbonyl, C_{1-4}alkoxycarbonyl, hydroxy-C_{2-4}-alkyloxy, dioxolanyl substituted with two C_{1-6}alkyl radicals, and a heterocycle selected from the group consisting of pyrrolidinyl, indolyl, imidazolyl, piperidinyl, piperazinyl, and pyridyl, wherein each of said heterocycle may optionally be substituted with up to two substituents independently selected from oxo and C_{1-6}alkyl.

11. A compound according to any of claims 1 - 8, wherein Q is Ar^2, C_{3-7}cycloalkyl, or C_{1-6}alkyl optionally substituted with Ar^2, with one or two hydroxyl groups, with C_{1-4}alkoxy, C_{1-4}alkylthio, aminocarbonyl, C_{1-4}alkoxycarbonyl, hydroxy-C_{2-4}alkyl-oxy, dioxolanyl substituted with two C_{1-6}alkyl radicals, or a heterocycle selected from pyrrolidinyl, indolyl, imidazolyl, piperidinyl, piperazinyl, and pyridyl, wherein each of said heterocycle may optionally be substituted with two substituents independently selected from oxo and C_{1-6}alkyl.

12. A compound according to any of claims 9 - 11, wherein Ar^2 is phenyl or phenyl substituted with 1, 2 or 3 substituents from halo, hydroxy, amino, cyano, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxy and aminosulfonyl.

13. A compound according to any of claims 9 - 11, wherein Ar^2 is phenyl or phenyl substituted with 1 or 2 substituents selected from amino, cyano, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl and aminosulfonyl.

14. A compound according to any of claims 9 - 11, wherein one of R^{2a} and R^{3a} is C_{1-6}alkyl and the other one of R^{2a} and R^{3a} is hydrogen;
in case R^{2a} is different from hydrogen then R^{2b} is C_{1-6}alkyl, and R^{3b} is hydrogen;
in case R^{3a} is different from hydrogen then R^{3b} is C_{1-6}alkyl, and R^{2b} is hydrogen.

15. A compound as claimed in any one of claims 1 to 14 for use as a medicine.

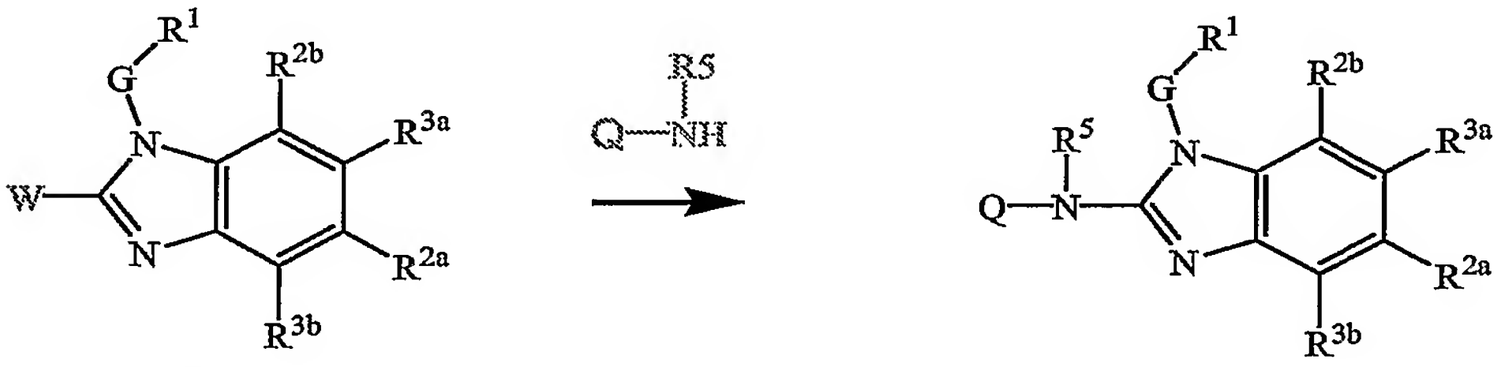
16. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 14.

17. A process for preparing a pharmaceutical composition as claimed in claim 16, said process comprising intimately mixing a pharmaceutical acceptable carrier with a therapeutically effective amount of a compound as claimed in any one of claims 1 to 16.

18. The use of a compound as claimed in any of claims 1 to 14 for the manufacture of a medicament for inhibiting RSV replication.

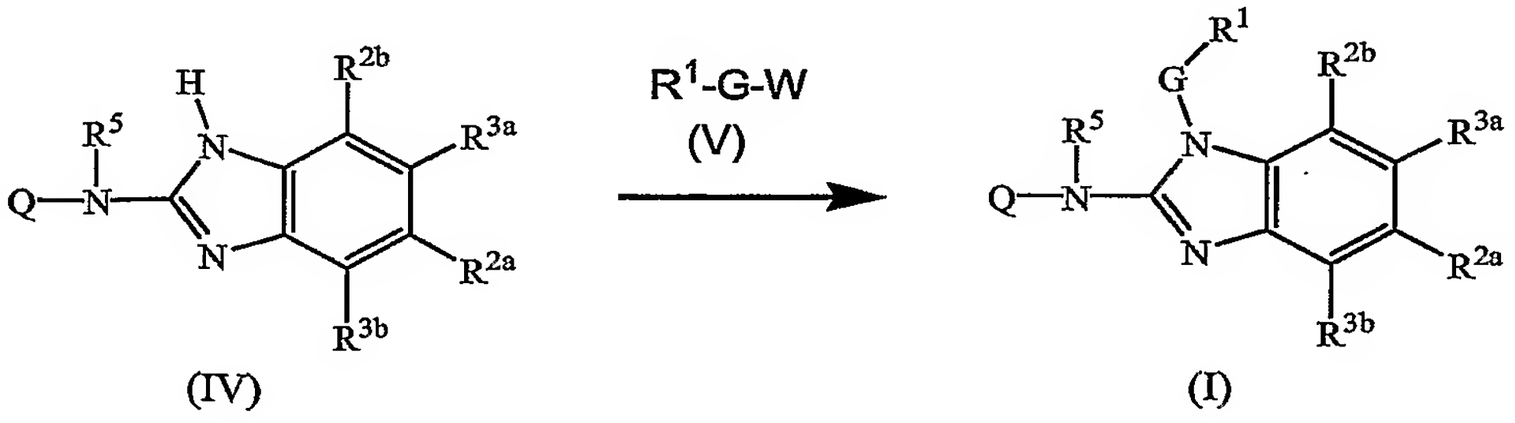
19. A process for preparing a compound as claimed in any of claims 1 to 14, said process comprising

(a) reacting an intermediate of formula (II) with a reagent (III) as in the following reaction scheme:



(II) (I)

(b) reacting an intermediate of formula (IV) with a reagent (V) as in the following reaction scheme:



(IV) (I)

wherein Q, G, R^1, R^{2a}, R^{2b} , R^{3a} , R^{3b}, R^5 are as claimed in any of claims 1 to 16; and optionally converting the thus obtained compounds of formula (I) into their pharmaceutically acceptable base-addition or acid addition salt form by treatment with a suitable base or acid and conversely treating the base-addition or acid addition salt form with an acid or a base to obtain the free form of the compound of formula (I).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/053617

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/06 A61K31/4184 C07D401/14 C07D405/14 A61P11/00
A61P31/12
//(C07D401/06,235:00,213:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/00611 A (JANSSENS FRANS EDUARD ;SOMMEN FRANCOIS MARIA (BE); ANDRIES KOENRAA) 4 January 2001 (2001-01-04) page 87; table 13 -----	1-19
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 March 2005	01/04/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Lauro, P

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/053617

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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[redacted] Information on patent family members

International Application No
[redacted]T/EP2004/053617

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